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略号一覧表

略号又は略称	名称及び内容
ABC	streptavidin-biotin-horseradish peroxidase complex（ストレプトアビジン-ビオチン-西洋ワサビペルオキシダーゼ複合体）
ADA	anti-drug antibody（抗薬物抗体）
ADCC	antibody-dependent cell-mediated cytotoxicity（抗体依存性細胞傷害）
APTT	activated partial thromboplastin time（活性化部分トロンボプラスチン時間）
AUC_{0-t}	area under the serum concentration versus time curve from time 0 to defined time point t（0 時間から t 時間までの血清中濃度－時間曲線下面積）
CDC	complement-dependent cytotoxicity（補体依存性細胞傷害）
CHO	Chinese hamster ovary（チャイニーズハムスター卵巣細胞）
C_{max}	maximum serum concentration（最高血清中濃度）
CNS	central nervous system（中枢神経系）
CTD	common technical document（コモンテクニカルドキュメント）
ECG	electrocardiogram（心電図）
EMA	European Medicines Agency（欧州医薬品庁）
FDA	Food and Drug Administration（米国食品医薬品局）
FITC	fluorescein isothiocyanate（フルオレセインイソチオシアナート）
GLP	good laboratory practice（医薬品の安全性に関する非臨床試験の実施の基準）
h	hour（時間）
HRP	horseradish peroxidase（西洋ワサビペルオキシダーゼ）
HuMab-CD38	a human IgG1 mAb that specifically binds human and cynomolgus monkey CD38（ヒト及びカニクイザルの CD38 に特異的に結合するヒト型 IgG1 モノクローナル抗体）
ICH	International Conference on Harmonisation（日米 EU 医薬品規制調和国際会議）
IFN-γ	interferon-gamma（インターフェロン γ）
IgA	immunoglobulin A（免疫グロブリン A）
IgG	immunoglobulin G（免疫グロブリン G）
IgG1κ	immunoglobulin G1 kappa（免疫グロブリン G1 kappa）
IgM	immunoglobulin M（免疫グロブリン M）
IHC	immunohistochemistry（免疫組織化学）
IL-6	interleukin-6（インターロイキン 6）
IND	Investigational New Drug（治験薬）
IRR	infusion related reaction（インフュージョン・リアクション）
IV	intravenous（静脈内）
KLH	keyhole limpet hemocyanin（スカシ貝ヘモシアニン）
mAb	monoclonal antibody（モノクローナル抗体）
MM	multiple myeloma（多発性骨髄腫）
NK	natural killer（ナチュラルキラー）
NOAEL	no observed adverse effect level（無毒性量）
PECAM	platelet endothelial cell adhesion molecule（血小板内皮細胞接着分子）
RBC	red blood cell（赤血球）
TNF-α	tumor necrosis factor-alpha（腫瘍壊死因子 α）
TK	toxicokinetics（トキシコキネティクス）

2.6.6 毒性試験の概要文

2.6.6.1 まとめ

ダラツムマブ（遺伝子組換え）は，CD38 に特異的に結合するヒト免疫グロブリン G1κ（IgG1κ）モノクローナル抗体（mAb）である【CTD 2.6.2.1.1 参照】。

毒性試験の一覧を表 2.6.6-1 に示す。反復投与毒性試験では単回投与毒性，局所刺激性，免疫毒性及び安全性薬理の評価項目を組み入れた。

表 2.6.6-1 ダラツムマブの毒性試験一覧表

試験の種類 投与期間(休薬期間)	動物種／ 試験系	投与方法 (投与頻度)	投与量 (mg/kg)	被験物質	GLP 適用	資料番号
反復投与毒性試験						
2 週間投与試験 (8 週間)	カニクイザル	静脈内 (週 1 回)	0, 20, 100 [a]	HuMab-CD38 [d]	非 GLP	参考資料 4.2.3.2.1
6 週間投与試験 (13 又は 15 週間)	チンパンジー	静脈内 (週 1 回)	0→5 [b] 0→25 [c]	ダラツムマブ	GLP	評価資料 4.2.3.2.2
その他の毒性試験						
組織交差反応性試験	カニクイザル 正常組織	*In vitro*	0, 0.2, 0.5, 1 μg/mL	HuMab-CD38 [d]	GLP	評価資料 4.2.3.7.7.1
組織交差反応性試験	チンパンジー 正常組織	*In vitro*	0.25, 1.25 μg/mL	ダラツムマブ	GLP	評価資料 4.2.3.7.7.2
組織交差反応性試験	ヒト正常組織	*In vitro*	0, 0.5, 1, 2 μg/mL	ダラツムマブ	GLP	評価資料 4.2.3.7.7.3

a Day 1 及び Day 8 に溶媒又は HuMab-CD38 を 30 分間かけて静脈内持続投与
b Day 0 に溶媒を投与した後，Day 7 にダラツムマブ 5 mg/kg を 30 分間かけて静脈内持続投与を行い，以後同様に週 1 回の頻度で Day 42 まで 6 週間投与
c Day 7 に溶媒を投与後，過剰なサイトカイン放出を予防する目的で Day 21 にダラツムマブ 10 mg を静脈内にボーラスで前投与し，その 24 時間後（Day 22）にダラツムマブ 25 mg/kg を 1 時間かけて静脈内持続投与。以後週 1 回の頻度で 30 分間の静脈内持続投与を Day 56 まで 6 週間実施
d 本試験は，ヒト及びカニクイザルの CD38 に特異的に結合するヒト型 IgG1 mAb である HuMab-CD38 を用いて実施

2.6.6.1.1 毒性試験に関する情報

ダラツムマブの毒性試験は日米 EU 医薬品規制調和国際会議（ICH）S6(R1)及び ICH S9 ガイドラインに従って実施し，主要な毒性試験は GLP に準拠して実施した。各試験の GLP 適用状況及び実施施設に関する情報は毒性試験の一覧表【CTD 2.6.7.1 参照】に示す。

毒性試験及び臨床試験で使用したダラツムマブのバッチは，遺伝子導入マウス及びハイブリドーマ技術を用いて作製し，標準的な懸濁培養法及び精製法を用いて，遺伝子組換えほ乳類細胞株［チャイニーズハムスター卵巣細胞（CHO）］で生産された。

カニクイザルを用いた 2 週間投与予備試験【CTD 4.2.3.2.1 参照】及び組織交差反応性試験【CTD 4.2.3.7.7.1 参照】では，CHO 株により生産された HuMab-CD38 を使用した。HuMab-CD38 は標準的な懸濁培養法と精製法を用いて生産された。

組織交差反応性試験【CTD 4.2.3.7.7.2，CTD 4.2.3.7.7.3 参照】及びチンパンジーを用いた 6 週間投与試験【CTD 4.2.3.2.2 参照】で使用されたダラツムマブの細胞株は同一であった。

2.6.6.1.2 薬理学的に適切な動物種の選択

ダラツムマブは，ヒト及びチンパンジーの CD38 に結合するが，マウス，ラット，ウサギ，ブタ，カニクイザル，アカゲザルなど毒性試験で一般に用いられる動物種の CD38 には結合しない【CTD 2.6.2.2.3 参照】。

HuMab-CD38 はヒト及びカニクイザルの CD38 と高い親和性で結合する mAb であり，ダラツムマブと同程度の抗体依存性細胞傷害（ADCC）作用を示す。しかしながら，ダラツムマブと HuMab-CD38 の間には以下に示すような作用の相違がある。すなわちダラツムマブと比較して，HuMab-CD38 は腫瘍細胞に対する *in vitro* 補体依存性細胞傷害（CDC）作用及び CD38 のシクラーゼ活性阻害作用が弱い【CTD 2.6.2.6.3 参照】。また，HuMab-CD38 はカニクイザルの赤血球（RBC），B 細胞及び T 細胞に対する結合性を有するが，ダラツムマブにその結合性はない。なお，ダラツムマブ及び HuMab-CD38 はいずれもヒトの RBC，B 細胞及び T 細胞に対する結合性が弱い【CTD 2.6.2.2.3.1 (4)参照】。

したがって，ダラツムマブの毒性を検討するため，薬理学的に適切な動物種としてチンパンジーを選択した。しかしチンパンジーは絶滅危惧種であるため，毒性評価に使用できる動物数が非常に少数である上，安楽死させて標的器官の重量測定及び病理組織学的検査を行うことはできない。以上の理由から，ダラツムマブの主要な毒性試験は，チンパンジーを用いた反復投与毒性試験，並びにチンパンジー及びヒトの正常組織を用いた組織交差反応性試験に限定した。なお，反復投与毒性試験の追加試験は米国食品医薬品局（FDA）及び欧州医薬品庁（EMA）に相談した上で，実施しなかった[1]。

2.6.6.1.3 単回投与毒性試験

単回投与毒性試験は実施しなかった。急性毒性は ICH S6 (R1)ガイドラインに従って反復投与毒性試験の一部として評価した。

カニクイザルに HuMab-CD38 を 20 及び 100 mg/kg の用量で単回静脈内投与したとき，死亡例はみられず，概略の致死量は 100 mg/kg 超であった。チンパンジーにダラツムマブを 5 及び 25 mg/kg の用量で単回静脈内投与したとき，5 mg/kg 投与群の 1 例が死亡したことから，概略の致死量は 5 mg/kg であった。

2.6.6.1.4 反復投与毒性試験

HuMab-CD38 の反復投与毒性は，カニクイザルに 20 及び 100 mg/kg の用量で週 1 回，2 週間静脈内持続投与することにより評価した。20 及び 100 mg/kg 投与群において貧血（ヘモグロビン濃度，RBC 数及びヘマトクリット値の減少）並びに CD38 を発現している CD4 陽性及び CD8 陽性 T 細胞の減少／枯渇が観察された。HuMab-CD38 のカニクイザル RBC への結合性は強いが，ダラツムマブのヒト RBC への結合性は弱い【CTD 2.6.2.2.3.1 (4) 参照】ことから，HuMab-CD38 を投与したカニクイザルで観察された貧血の臨床的意義は低いと考えられる。HuMab-CD38 の

[1]海外規制当局は，チンパンジーが薬理学的に毒性評価に適した唯一の動物種であることから，これ以上反復投与毒性試験を実施する必要はないことに合意している（[redacted]年[redacted]月[redacted]日の FDA との IND 前相談議事録，又は EMA の[redacted]年[redacted]月[redacted]日付科学的助言）。

RBC への影響は可逆的であった。本試験における HuMab-CD38 の無毒性量（NOAEL）は 20 mg/kg 未満であった。

ダラツムマブの反復投与毒性は，チンパンジーに 5 及び 25 mg/kg の用量で週 1 回，6 週間静脈内持続投与することにより評価した。主な毒性所見はサイトカイン放出反応及び血小板減少症であった。サイトカイン放出反応はダラツムマブ初回投与時に認められたが，以後の投与では発現しなかった。低用量（5 mg/kg）群のチンパンジー1 例が初回投与後に死亡した。高用量（25 mg/kg）群においてサイトカインの過剰放出反応が生じるのを予防するため，ダラツムマブ初回持続投与の 24 時間前にダラツムマブ 10 mg を静脈内投与した。この処置により高用量群では初回投与後の反応が軽度になった。サイトカイン放出反応は臨床ではインフュージョン・リアクション（IRR）に相当すると考えられ，本剤の臨床試験では被験者に対して副腎皮質ステロイド，解熱鎮痛剤及び抗ヒスタミン剤の前投薬を行うとともに，本剤の投与調節を行うことにより，ほとんどの IRR は臨床的に管理可能であった【CTD 2.7.4.2.1.5 (1)参照】。チンパンジーに認められた血小板減少症は血中からダラツムマブが消失するに伴い，正常に回復した。ヒトとチンパンジーの血小板に対するダラツムマブの結合には種差が認められた【CTD 2.6.2.3.2 参照】。ヘルパーT 細胞，ナチュラルキラー（NK）細胞及び B 細胞の減少はダラツムマブの薬理作用と関係していると考えられる。本試験におけるダラツムマブの NOAEL は 5 mg/kg 未満であった。

2.6.6.1.5 その他の毒性試験

2.6.6.1.5.1 免疫毒性試験

独立した試験は実施していないが，反復投与毒性試験の中で免疫毒性に関するパラメータを評価した。カニクイザルを用いた HuMab-CD38 の 2 週間静脈内持続投与試験において検討したスカシ貝ヘモシアニン（KLH）による液性免疫機能検査では，KLH 特異的な血清中免疫グロブリン G（IgG）及び免疫グロブリン M（IgM）抗体価の減少が認められ，液性免疫反応の抑制が示唆された。

2.6.6.1.5.2 組織交差反応性試験

組織交差反応性試験として，ダラツムマブとヒト組織及びチンパンジー組織との結合性，並びに HuMab-CD38 とカニクイザル組織との結合性を評価した。ダラツムマブとの特異的結合が認められた組織は，ほとんどがリンパ系組織であった。なお，いずれの種においてもダラツムマブとの結合が複数組織の細胞質に認められたが，mAb は細胞内に移行しないことから，細胞質に認められた mAb 結合に毒性学的及び臨床的意義はない。

2.6.6.2 単回投与毒性試験

本薬の単回投与毒性試験は実施していない。急性毒性は ICH S6 (R1)ガイドラインに従って反復投与毒性試験の一部として評価した。

カニクイザルに HuMab-CD38 を 20 及び 100 mg/kg の用量で単回静脈内投与したとき，死亡例はみられず，概略の致死量は 100 mg/kg 超であった。チンパンジーにダラツムマブを 5 及び

25 mg/kg の用量で単回静脈内投与したとき，5 mg/kg 投与群の 1 例が死亡したことから，概略の致死量は 5 mg/kg であった。

2.6.6.3 反復投与毒性試験

ダラツムマブの反復投与毒性を評価するにあたって，ダラツムマブのほか，カニクイザルの CD38 に結合する mAb である HuMab-CD38 を使用した。

本薬の反復投与毒性試験として，カニクイザルを用いた HuMab-CD38 の 2 週間静脈内持続投与試験（非 GLP 試験）及びチンパンジーを用いたダラツムマブの 6 週間静脈内持続投与試験（GLP 試験）を実施した。

なお，反復投与毒性試験では標準的な毒性学的評価に加えて，安全性薬理［心血管系及び中枢神経系（カニクイザル及びチンパンジー）並びに呼吸系（チンパンジー）に対する作用］，免疫毒性及び免疫原性についても評価した。

2.6.6.3.1 カニクイザルを用いた HuMab-CD38 の 2 週間反復静脈内持続投与及び 8 週間回復性試験（毒性及び薬物動態試験の予備検討）（非 GLP 試験）

【参考資料 4.2.3.2.1】

【試験方法】

1 群雌雄各 2 例のカニクイザルに HuMab-CD38 を 0（溶媒），20 及び 100 mg/kg の用量（10 mL/kg）で 2 回（投与日：Day 1 及び 8），1 回につき 30 分間かけて静脈内持続投与した後，8 週間休薬することにより，HuMab-CD38 の毒性及び薬物動態プロファイルを検討した。用量はカニクイザルを用いた用量設定試験の結果に基づいて設定した。試験開始時のサルの月齢は 14～21 カ月齢，体重は雄が 2.2～2.4 kg，雌が 1.8～2.1 kg であった。なお，本試験では前投与は実施しなかった。

最終投与日の 3 日後（Day 11）に主試験群（1 例/性/群），8 週間休薬後（Day 64）に回復試験群（1 例/性/群）をそれぞれ剖検し，毒性所見の可逆性及び持続性，並びに遅延毒性の発現有無を評価した。試験デザインを表 2.6.6-2 に示す。

本試験では一般状態観察，理学的検査（腹部触診，胸部聴診及び生検部位の視診），眼科学的検査，体重測定，血液学的検査，血液生化学的検査，血液凝固系検査，尿検査，剖検，骨髄塗抹検査，器官重量測定，病理組織学的検査，血清中 HuMab-CD38 濃度測定及び血清中抗 HuMab-CD38 抗体測定を実施した。また，安全性薬理の評価項目として，心血管系は心電図（ECG）検査及び心拍数測定，中枢神経系（CNS）は一般状態観察及び体温測定を実施した。そのほか，血清中抗 KLH 抗体価測定，直接クームス試験，末梢血リンパ球サブセット解析（フローサイトメトリー），リンパ節及び骨髄の生検（フローサイトメトリー），並びに免疫組織化学的解析（IHC 解析）を実施した。

表 2.6.6-2 カニクイザルを用いた HuMab-CD38 の 2 週間静脈内持続投与及び 8 週間回復性試験の試験デザイン

群	投与量 (mg/kg)	薬液濃度 (mg/mL)	使用動物数		剖検動物数（個体番号）			
			投与日：Day 1，8 静脈内持続投与（30 分間）		主試験群 ［剖検：Day 11］		回復試験群 ［剖検：Day 64］	
			雄	雌	雄	雌	雄	雌
1	0 (溶媒)	0	2	2	1 (1M)	1 (7F)	1 (2M)	1 (8F)
2	20	2	2	2	1 (3M)	1 (9F)	1 (4M)	1 (10F)
3	100	10	2	2	1 (5M)	1 (11F)	1 (6M)	1 (12F)

【結果】

試験結果は毒性試験概要表に示す【CTD 2.6.7.6 参照】。試験期間中に死亡例はみられなかった。HuMab-CD38 投与に起因するサイトカイン放出症候群の徴候及びその他の一般状態の変化はみられず，体重，理学的検査，眼科学的検査，体温，ECG 及び尿検査にも，HuMab-CD38 投与の影響は認められなかった。

血液学的検査では，20 及び 100 mg/kg 投与群でヘモグロビン濃度，RBC 数及びヘマトクリット値の減少，網状赤血球数の増加が Day 8 から Day 28 まで認められた。RBC 数は，100 mg/kg 投与群で Day 21 に試験前値の 39%（雄）及び 61%（雌）まで減少し，100 mg/kg 投与群の雄では Day 28 でも RBC 数の減少が認められた。20 及び 100 mg/kg 投与群でリンパ球数減少による白血球数の減少が Day 2 から Day 36 までみられた。

血液生化学的検査では，20 及び 100 mg/kg 投与群で総ビリルビンの増加が Day 2 から Day 15 まで認められた。20 及び 100 mg/kg 投与群で IgM 濃度の減少が Day 15 から休薬期間終了時までみられた。また，100 mg/kg 投与群で免疫グロブリン A（IgA）及び IgG 濃度の減少が Day 15 以降認められたが，休薬期間終了時にほぼ試験前値の濃度まで回復した。

剖検では，胸腺の小型化が 100 mg/kg 投与群で認められたが，休薬期間終了時には同所見は認められなかった。

器官重量測定では，100 mg/kg 投与群で胸腺重量の減少がみられたが，休薬期間終了時までに回復した。

病理組織学的検査では，20 mg/kg 投与群で軽度～中等度の胸腺萎縮，100 mg/kg 投与群で高度の胸腺萎縮が認められた。20 及び 100 mg/kg 投与群では，下顎リンパ節，腸間膜リンパ節，パイエル板及び脾臓のリンパ濾胞萎縮又はリンパ球枯渇が認められたが，特に 100 mg/kg 投与群の雄で顕著にみられた。休薬期間終了時でも，100 mg/kg 投与群の雌で軽微な胸腺萎縮が，100 mg/kg 投与群の雄で腸間膜リンパ節の軽微なリンパ球枯渇が認められた。100 mg/kg 投与群の雌の脊髄に軽度の多巣性脊髄炎が認められた。休薬期間終了時に，20 mg/kg 投与群の雄の脊髄，並びに 100 mg/kg 投与群の雄の脊髄及び坐骨神経に，軽微な限局性炎症細胞浸潤が認められた。

骨髄塗抹検査の結果は，末梢血に認められた変化とおおむね一致していた。20 mg/kg 投与群の雌雄及び 100 mg/kg 投与群の雌で正赤芽球の増加が Day 11 に認められ，20 mg/kg 投与群の雌で分裂期前骨髄球の増加がみられた。対照群が正常な骨髄の特徴を示したのに対し，HuMab-CD38 投与群では全例がリンパ球減少を示した。休薬期間終了時には，対照群及び HuMab-CD38 投与群とも，すべての細胞系について正常な細胞密度及び形態が観察された。

末梢血のフローサイトメトリーでは，20 及び 100 mg/kg 投与群において CD38 を発現している CD4 陽性及び CD8 陽性 T 細胞の高度な減少又は枯渇が Day 8 に認められ，100 mg/kg 投与群では Day 1 でも同細胞の減少が認められたが，いずれも休薬期間中に増加し回復傾向を示した。20 及び 100 mg/kg 投与群では，CD38 を発現しているエフェクターNK 細胞（CD16 陽性 CD38 陽性 CD8 陽性）の枯渇が認められ，CD16 陽性 CD8 陽性 NK 細胞でも枯渇がみられたことから，多数のエフェクターNK 細胞が CD38 を発現していることが示唆された。また，両投与群では，CD27 を発現していない成熟 B 細胞（CD27 陰性 CD21 陽性 CD40 陽性 CD20 陽性）の細胞数も高度に減少した。この細胞数減少は，20 mg/kg 投与群よりも 100 mg/kg 投与群で早期に認められ（細胞数の減少開始時期はそれぞれ Day 8 及び Day 1），同細胞の減少は，いずれの投与群でも休薬期間終了時までに回復しなかった。両投与群では，CD38 を発現しているメモリーB 細胞（CD27 陽性 CD38 陽性 CD20 陽性）が，CD38 を発現している B 細胞，CD27 を発現している B 細胞と同様，高度に枯渇したが，休薬期間終了時までに完全には回復しなかった。なお，単球の減少が認められたが，軽度かつ一過性の変化であったことから，HuMab-CD38 投与に関連した所見ではないと判断した。

リンパ節のフローサイトメトリーでは，両投与群で CD38 を発現している CD4 陽性 T 細胞が減少したが，末梢血中の同細胞ほどの減少ではなかった。CD38 を発現している CD8 陽性 T 細胞が，より顕著に枯渇した。CD4 陽性 T 細胞と CD8 陽性 T 細胞の減少は，両投与群でおおむね類似していた。なお，リンパ節で NK 細胞が全細胞中に占める割合は 1%未満であることから，NK 細胞に対する影響は評価できなかった。リンパ節で CD27 を発現していない成熟 B 細胞（CD27 陰性 CD21 陽性 CD40 陽性 CD20 陽性）の割合はほとんど変化せず，他のすべての B 細胞も同様でほとんど変化がみられなかった。CD14 陽性の単球（及びサブセット）が全細胞中に占める割合は 2%未満であったことから，更なる評価はできなかった。

直接クームス試験では，Day 8 は 20 及び 100 mg/kg 投与群の全例，Day 28 は 20 mg/kg 投与群の雄及び 100 mg/kg 投与群の雌雄で，HuMab-CD38 と RBC との結合が認められた。休薬期間終了時でも 100 mg/kg 投与群の雌 1 例で RBC との結合が認められた。

血清中抗 KLH 特異的 IgG 及び IgM 抗体価の上昇は休薬期間中の Day 55 まで HuMab-CD38 によって抑制されたが，Day 55 に 3 回目の免疫付与を行うと，両投与群で IgG 濃度が Day 64 までに正常値まで増加し，20 mg/kg 投与群では IgM 濃度が試験前値に回復した。

IHC 解析では，HuMab-CD38 がリンパ組織の標的部位に結合することが確認された。HuMab-CD38 の結合が剖検時まで動物の組織内で維持されていた。HuMab-CD38 で前処理をしたとき，20 及び 100 mg/kg 投与群の全例で，リンパ濾胞外の組織，胸腺，腎糸球体及び骨髄等の広範な組織に染色が認められたことから，これらの組織に CD38 を発現している細胞が存在することが示唆された。

【トキシコキネティクス】

TK 評価によって，Day 1 及び 8 における HuMab-CD38 の全身曝露量は 20 から 100 mg/kg まで用量増加に伴って増加することが示された。HuMab-CD38 の持続投与開始後 0.5～3.5 時間に高い血清中濃度が認められた。本試験ではいずれの TK パラメータにも性差はみられなかった（表 2.6.6-3）【CTD 2.6.7.3 参照】。

20 mg/kg 投与群では，休薬期間に抗 HuMab-CD38 抗体（ADA）が検出された。ADA 反応が 20 mg/kg 投与群だけに認められ，100 mg/kg 投与群にみられなかった理由として，血清中に高濃度で存在する HuMab-CD38 が抗体検出に干渉した可能性が考えられる。

表 2.6.6-3 カニクイザルを用いた HuMab-CD38 の 2 週間静脈内持続投与及び 8 週間回復性試験における血清中曝露量（C_{max} 及び AUC_{0-t}）

投与量[a, b] (mg/kg)	群	個体番号	投与日	C_{max}[c] (μg/mL)	AUC_{0-t}[c] (μg·h/mL)
20	2 (主試験)	3M	Day 1	1,920.0	35,452.6[e]
20	2 (回復試験)	4M[d]	Day 1	682.0	29,122.4[e]
20	2 (主試験)	9F	Day 1	416.0	21,807.9[e]
20	2 (回復試験)	10F[d]	Day 1	498.0	33,319.3[e]
20	2 (主試験)	3M	Day 8	707.0	19,698.1[f]
20	2 (回復試験)	4M[d]	Day 8	815.0	43,435.5[g]
20	2 (主試験)	9F	Day 8	481.0	14,784.9[f]
20	2 (回復試験)	10F[d]	Day 8	558.0	32,000.9[h]
100	3 (主試験)	5M	Day 1	2,880.0	138,086.5[e]
100	3 (回復試験)	6M	Day 1	3,760.0	237,890.0[e]
100	3 (主試験)	11F	Day 1	2,880.0	196,521.5[e]
100	3 (回復試験)	12F	Day 1	3,980.0	189,266.5[e]
100	3 (主試験)	5M	Day 8	3,810.0	101,670.8[f]
100	3 (回復試験)	6M	Day 8	3,460.0	403,617.4[i]
100	3 (主試験)	11F	Day 8	3,880.0	110,092.3[f]
100	3 (回復試験)	12F	Day 8	3,820.0	703,593.1[j]

a ヒト及びカニクイザルの CD38 に特異的に結合するヒト IgG1 mAb である HuMab-CD38 を動物に投与した。
b 動物（2 例/性/群）に HuMab-CD38 を週 1 回の頻度で 2 週間，1 回につき 30 分間かけて静脈内持続投与（Day 1 及び 8 に投与）
c TK 分析用血液試料は以下の時点で採取した。
Day 1： 持続投与前，持続投与直後並びに 0.5，1.5，3，6，12，24，48，72 及び 120 時間後
Day 8（主試験群）： 持続投与前，持続投与直後並びに 0.5，1.5，3，6，12，24 及び 48 時間後
Day 8（回復試験群）： 持続投与前，持続投与直後，0.5，1.5，3，6，12，24，48，72 及び 120 時間後，並びに Day 15，18，21，24，28，32，36，40，50 及び 64
d 20 mg/kg 回復試験群の雄（4M）は Day 21，36，50 及び 64，雌（10F）は Day 21，36 及び 64 に抗体産生陽性を示した。
e $AUC_{0-168hr}$, f AUC_{0-48hr}, g $AUC_{0-Day\ 18}$, h $AUC_{0-Day\ 15}$, i $AUC_{0-Day\ 40}$, j $AUC_{0-Day\ 50}$

【結論】

カニクイザルに HuMab-CD38 を 20 及び 100 mg/kg の用量で 2 週間静脈内持続投与したとき，両投与群に貧血（ヘモグロビン濃度，RBC 数及びヘマトクリット値の減少），末梢血及びリンパ節中の CD38 陽性細胞の減少／枯渇，並びに胸腺，リンパ節及び脾臓のリンパ濾胞萎縮又はリンパ球枯渇が認められた。いずれの所見も 8 週間の休薬期間中に，完全に回復又は回復過程にあることが示唆された。本試験における HuMab-CD38 の NOAEL は 20 mg/kg 未満であった。

2.6.6.3.2　チンパンジーを用いたダラツムマブの 6 週間反復静脈内持続投与及び 13 又は 15 週間回復性試験（GLP 試験）

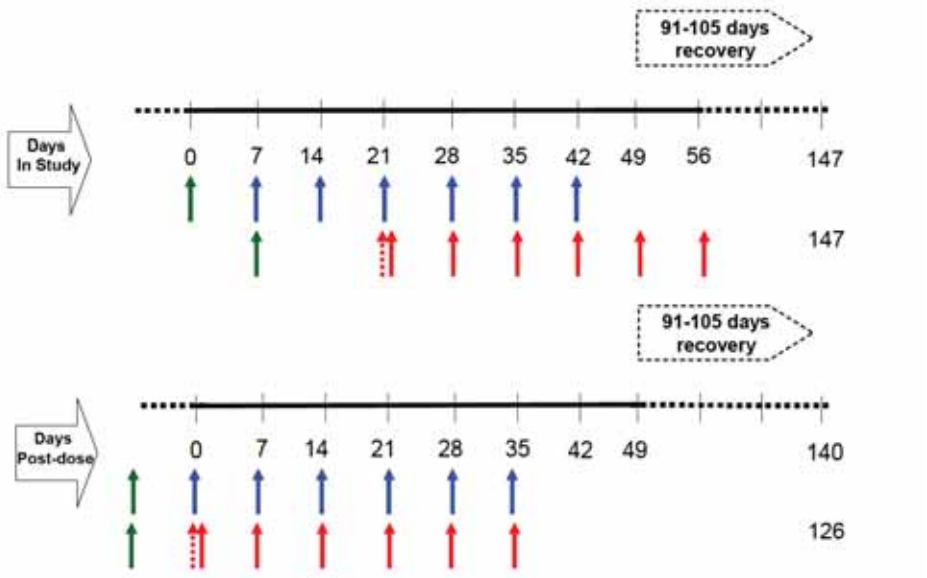
【評価資料 4.2.3.2.2】

【試験方法】

1 群雌雄各 1 例のチンパンジーにダラツムマブを 5 及び 25 mg/kg の用量で 1 週間ごとに 6 回，1 回につき 30 分間又は 1 時間かけて静脈内持続投与した後，それぞれ 15 週間（105 日間）及び 13 週間（91 日間）休薬することにより，有害作用の可逆性，持続性及び遅延発現の評価，並びに末梢血，骨髄及びリンパ節中の CD38 陽性標的細胞の枯渇及び回復性を検討した。用量は先に実施したカニクイザル 2 週間投与試験の結果に基づいて設定した。

当初，1 群雌雄各 1 例を 2 群に無作為に割付けていたが，2 回目投与後に，第 1 群の雌（95A015）を鎮静させる際，下腹部裂傷（本薬投与と無関係）を負ったことから本薬投与を中止し，代わりに別の雌（92A016）を第 1 群に加えた。試験デザインを図 2.6.6-1 に示す。試験開始時，動物は 10～15 年齢，体重は 42.24～55.91 kg であった。

最初の試験計画では，溶媒を 30 分間かけて静脈内持続投与した後，ダラツムマブ 5 及び 25 mg/kg の 30 分間静脈内持続投与を週 1 回の頻度で 6 週間行う予定であった。しかし，サイトカイン放出症候群と考えられる所見が第 1 群（5 mg/kg）に観察されたため，試験計画書を変更して，第 2 群（25 mg/kg）ではダラツムマブを初回持続投与する 24 時間前（Day 21）に，ダラツムマブ 10 mg を静脈内にボーラスで前投与した後，Day 22 に 25 mg/kg を静脈内持続投与（初回のみ持続投与時間を 1 時間に延長）することにした。また，当初設定されていた休薬期間は 8 週間であったが，血小板数減少の回復性を確認するために，低及び高用量群の休薬期間をそれぞれ 15 及び 13 週間に延長した。



注：緑の矢印は溶媒投与日，青の矢印は低用量（5 mg/kg）のダラツムマブ投与日，赤の矢印は高用量（25 mg/kg）のダラツムマブ投与日を示す。破線の矢印はダラツムマブ 10 mg/例の前投与日を示す。
上図の Days in Study の数字は，当初の試験計画における試験開始日からの日数（初回溶媒投与日を Day 0）

図 2.6.6-1 試験計画書に規定された投与日（上図）とダラツムマブ初回投与日を Day 0 とした場合の投与後日数（下図）の関係を示す説明図

表 2.6.6-4 チンパンジーを用いたダラツムマブの 6 週間静脈内持続投与試験の試験デザイン及び投与スケジュール

群	個体番号	性別	Day [a]	被験物質	投与量	投与経路／投与方法	投与回数
1[b]	96A009	M	0	溶媒	0	IV, 30 分間持続	6
			7, 14, 21, 28, 35, 42	ダラツムマブ	5 mg/kg	IV, 30 分間持続	
	95A015[c]	F	0	溶媒	0	IV, 30 分間持続	2
			7, 14	ダラツムマブ	5 mg/kg	IV, 30 分間持続	
	92A016[d]	F	0	溶媒	0	IV, 30 分間持続	1
			7	ダラツムマブ	5 mg/kg	IV, 30 分間持続	
2[e]	96A015	M	7	溶媒	0	IV, 30 分間持続	6
			21	ダラツムマブ	10 mg/例	IV（ボーラス）	
			22	ダラツムマブ	25 mg/kg	IV, 1 時間持続	
			28, 35, 42, 49, 56	ダラツムマブ	25 mg/kg	IV, 30 分間持続	
	96A017	F	7	溶媒	0	IV, 30 分間持続	6
			21	ダラツムマブ	10 mg/例	IV（ボーラス）	
			22	ダラツムマブ	25 mg/kg	IV, 1 時間持続	
			28, 35, 42, 49, 56	ダラツムマブ	25 mg/kg	IV, 30 分間持続	

a Day 0 又は Day 7 を溶媒投与日としたため，動物全例の Day 0 又は Day 7 の暦日は同一ではない。
b 第 1 群では Day 0 に溶媒を投与した後，Day 7 にダラツムマブ 5 mg/kg を 30 分間かけて静脈内持続投与した。投与は Day 42 まで週 1 回の頻度で 6 週間行い，その後 15 週間の休薬期間を設定した。
c 個体番号 95A015 は，ダラツムマブ投与と無関係の下腹部裂傷のため Day 15 に投与を中止した。
d 個体番号 92A016（個体番号 95A015 の代替動物）は Day 7 の初回投与後に死亡したが，代替動物は設定しなかった。
e 第 2 群では Day 7 に溶媒を投与した。過剰なサイトカイン放出を予防するため，Day 21 にダラツムマブ 10 mg を静脈内にボーラスで前投与し，24 時間後（Day 22）にダラツムマブ 25 mg/kg を 1 時間かけて静脈内持続投与した。投与は Day 56 まで週 1 回の頻度で 6 週間行った。その後 13 週間の休薬期間を設定した。

本試験では一般状態観察，眼科学的検査，体重測定，摂餌量測定，血液学的検査，血液生化学的検査，血液凝固系検査，直接抗グロブリン試験，尿検査，血清中ダラツムマブ濃度測定及び血清中抗ダラツムマブ抗体測定，並びに剖検及び病理組織学的検査（死亡例のみ）を実施した。また，安全性薬理の評価項目として，心血管系は ECG，血圧及び脈拍数，CNS は一般状態観察及び体温測定，呼吸系は呼吸数の測定を実施した。そのほか末梢血，骨髄及びリンパ節のフローサイトメトリー，皮膚，鼠径リンパ節及び骨髄の生検並びに IHC 解析を実施した。

【結果】

試験結果は毒性試験概要表に示す【CTD 2.6.7.7 参照】。眼科学的検査，体重，摂餌量，直接抗グロブリン試験，尿検査，ECG，血圧，脈拍数，体温，呼吸数及び生検試料（皮膚，鼠径リンパ節及び骨髄）の所見に，ダラツムマブ投与に関連した変化は認められなかった。

第 1 群では，全例が初回の 5 mg/kg 静脈内持続投与中にサイトカイン放出反応を示し，雌 1 例（個体番号 92A016）が死亡した。

一般状態の変化として，死亡動物は重度の反応（気管及び副鼻腔粘液の産生増加，くしゃみ，粘膜蒼白及び努力性呼吸）を発現した後，排便，並びに気管及び鼻孔からの泡沫状液体の大量排出を示し，投与後約 1.5 時間に呼吸が停止し死亡に至った（致死性肺水腫による）。この個体から投与後 1.5 時間及び剖検前に採取した血液試料中に，腫瘍壊死因子 α（TNF-α），インターロ

イキン 6（IL-6），インターフェロンγ（IFN-γ）が検出された。投与前及び投与終了時に採取した試料ではいずれも定量下限未満であった。

死亡動物（92A016）では，剖検で肺の過膨張及び浮腫，肺の炭粉沈着巣，左心室肥厚，右心室表面の慢性梗塞（瘢痕），胃と腸管ループの癒着が認められた。肺への液体貯留が死亡原因と考えられ，ダラツムマブ投与によって誘発された急性アナフィラキシーによる可能性が高い。病理組織学的検査では高度な所見は認められなかった。主な所見として肺細気管支周囲に肺水腫が認められ，生存期間中に肺血管から滲出があったものと示唆された。

第 1 群の生存例，雌雄各 1 例（個体番号 95A015 及び 96A009）でも，初回持続投与の開始後約 5 分（投与液量：17 mL）に気管粘液及び鼻汁の産生が増加した。また雄（個体番号 96A009）は投与開始後約 10 分（投与液量：33 mL）及び約 30 分に排便がみられた。雌雄各 1 例は回復し，以後の投与時に上記症状を発現しなかった。

第 2 群の雌（96A017）では，10 mg の前投与後に大量の粘液産生及び鈍麻がみられ，25 mg/kg の初回持続投与の開始後約 15 分（投与液量 25 mL）に軽度のくしゃみ及び粘液産生，開始後約 26 分（投与液量 44 mL）に粘膜蒼白が認められた。一方，第 2 群の雄（96A015）では，前投与後に一般状態の変化は認められなかったが，25 mg/kg の初回持続投与の開始後約 12 分（投与液量 20 mL）に，粘液の産生増加及びくしゃみ（軽度のサイトカイン放出症候群の徴候）が認められた。くしゃみは投与開始後約 30 分（投与液量 50 mL）には治まったものの，粘液増加は投与後 30 分でも気管に認められ，更に投与後 37 分には排便もみられた。以後の投与では，第 2 群にサイトカイン放出症候群の徴候は認められなかった。

第 2 群では，試験期間中に軟便がほぼ全例で散発的に認められ，休薬期間中も，より重度の胃腸障害が認められた。第 2 群の雄（96A015）では Day 86（最終投与後 30 日）から Day 106（最終投与後 50 日）まで下痢が長期間発現し，Day 105 には血便が認められた。さらに食欲低下及び活動性低下／抑うつも認められ，Day 105 以降も軟便が観察された。第 2 群の雌（96A017）では，Day 103～105（最終投与後 47～49 日）に下痢及び食欲低下がみられ，下痢，軟便及び食欲低下は試験終了時まで散発的に認められた。病理組織学的検査では下痢の原因を特定できなかったことから，被験物質が胃腸障害の要因である可能性を否定できない。そのほかには投与に関連した一般状態の変化は観察されなかった。

血液学的検査では，両投与群の全例が投与期間中に有意な血小板減少症を示した。第 1 群の雄（96A009）では，血小板数の漸減が初回持続投与後 24 時間から始まり，5 回目の投与後 24 時間には試験前値の 22%まで減少した。血小板数は，その後の休薬により Day 71（最終投与後 29 日）までに試験前値の 56%に回復した後，Day 98（最終投与後 56 日）には試験前値とほぼ同じになり，Day 98～147（最終投与後 105 日）の期間は試験開始前とほぼ同じレベルまで回復した。第 1 群の雌（95A015）の血小板数は，2 回目投与後 24 時間に試験前値の 46%に減少したが，2 回目投与の 3 週間後には試験前値を超えるレベルに回復した。

第 2 群の血小板数減少は第 1 群より顕著で，ダラツムマブ 10 mg を前投与した 24 時間後から始まり，投与期間中及び投与終了後も持続した。第 2 群の 2 例では，Day 112（最終投与後 56 日）に試験前値の 2%（雄）及び 4%（雌）まで血小板数が減少した。その後，血小板数は増加し，Day 147（最終投与後 91 日）までに雌（96A017）及び雄（96A015）の血小板数はそれぞれ試験前値の 65%及び 72%まで回復した。骨髄にダラツムマブ反復投与の影響が認められていないこと

から，血小板減少症の原因は血中の血小板の破壊／骨髄からの放出障害によるものと考えられる。いずれの投与群も血小板数が試験前値に回復したのは，末梢血中のダラツムマブ濃度が減少した後と考えられる（図 2.6.6-2）。いずれの群でも，投与期間中に血液中の好中球比率の増加及びリンパ球比率の減少が認められた。

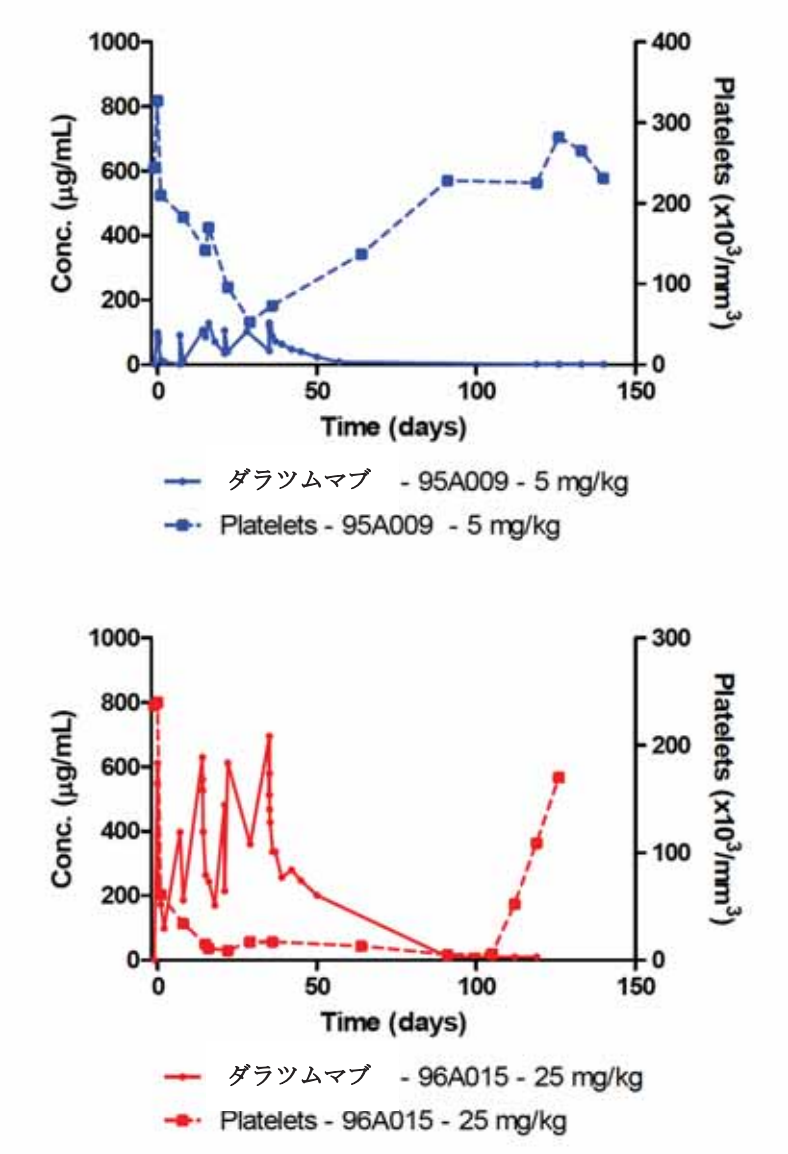


図 2.6.6-2 チンパンジーにダラツムマブ投与後の血清中ダラツムマブ濃度及び血小板数の推移
5 mg/kg 群（上図）及び 25 mg/kg 群（下図）

血小板数は減少したものの，生検試料の採取後に，自傷行為及び生検部位の開口行為が試験期間中，繰り返し観察された後でも，出血時間の延長，過度の出血又はその他の合併症は認められなかった。RBC 及びヘモグロビン濃度は，いずれの個体でも溶媒投与後 24 時間から減少し始め，投与期間中及び投与終了後も持続した。この軽度の貧血は，血液試料の頻回採取，複数回の生検実施，血液流出（消化管出血）及びダラツムマブ投与の影響が重なった結果，生じた影響である可能性が考えられる。5 mg/kg 投与群では，すべての RBC パラメータが休薬期間終了時までに試

験前値にほぼ回復した。25 mg/kg 投与群の RBC パラメータは休薬期間終了時では試験前値より低値であったが，Day 112～147（最終投与後 56～91 日）の期間で徐々に増加した。

血液生化学的検査では，両投与群において肝酵素（アスパラギン酸アミノトランスフェラーゼ，アラニンアミノトランスフェラーゼ，乳酸脱水素酵素）の上昇が投与翌日（溶媒投与を含む）に認められた。肝酵素の上昇が溶媒投与時にも認められたことから，本薬投与と関連した所見ではなく，長時間の鎮静又は動物の取扱いに起因する所見であると判断した。同様に，トリグリセリドの上昇も動物の取扱い又は鎮静に関連した所見である可能性が考えられた。25 mg/kg 投与群の雄（96A015）では，カリウム（初回投与後 24 時間から Day 126 まで）及び総タンパク（2 回目投与後 24 時間から Day 133 まで）の軽度減少が認められた。いずれの投与群でも全例が試験開始前より低い IgM 濃度を示した（初回投与後 24 時間から Day 147 まで）。IgG 濃度は全例が試験前値から徐々に減少した（初回投与後 24 時間から始まり投与期間中及び投与終了後も持続）。C-反応性タンパクの増加は，第 1 群では 2 例とも初回投与後 24 時間に認められ，第 2 群では 2 例とも溶媒投与後 24 時間から投与期間を通して認められた。すべてのパラメータは休薬期間中に試験前値又は正常範囲内に回復した。

血液凝固系検査では，両投与群の全例の大部分の測定ポイントで，初回投与後，活性化部分トロンボプラスチン時間（APTT）の中等度延長が認められた。第 1 群の雄（96A009）の APTT は Day 71 までに試験前値に回復した。第 2 群では APTT の軽度延長が Day 147 まで持続した。この APTT 延長は，全例が試験期間中に示した血小板減少症と関連している可能性が考えられる。プロトロンビン時間には，ダラツムマブ投与の影響は認められなかった。フィブリノゲン濃度は全例のほとんどすべての測定ポイントで試験前値より増加したが，採血及び生検による組織損傷に起因するものと考えられた。

末梢血のフローサイトメトリーでは，25 mg/kg 投与群でダラツムマブ投与に起因する単核球サブセットの細胞数の変化が最も高頻度に観察された。この変化にはダラツムマブ陽性ヘルパーT 細胞（投与期間及び休薬期間），NK 細胞（休薬期間）及び B 細胞（投与期間：一過性変化）の減少が認められた。他のほとんどの細胞は，毒性学的意義のある変化を示さなかった。

骨髄のフローサイトメトリーでは，5 及び 25 mg/kg 投与群で，ダラツムマブ投与に起因する単核球サブセットの細胞数の変化が観察されたが，ほとんどの変化に明らかな用量相関性は認められなかった。骨髄細胞の変化は概して単球に限られ，いずれの投与群でも大部分の CD14 陽性細胞の減少によるものであったが，Day 71 又は Day 85（第 1 群又は第 2 群への最終投与後約 1 カ月）～Day 98 の期間のみに認められた。

リンパ節のフローサイトメトリーでは，25 mg/kg 投与群でダラツムマブ投与に起因する単核球サブセットの細胞数の変化が最も高頻度に観察された。ヘルパーT リンパ球，細胞傷害性／サプレッサーT リンパ球，NK 細胞及び白血球において，細胞サブセットの構成比にダラツムマブ投与による変化が認められ，ダラツムマブと結合する細胞と一致した。上記細胞は Day 43 又は Day 57（第 1 群又は第 2 群への最終投与後 1 日）～Day 126 の期間に，顕著な減少が最も高頻度に認められ，Day 147 までに試験開始前の構成比に回復した。

【トキシコキネティクス】

TK 評価において，ダラツムマブの全身曝露量は 5 から 25 mg/kg まで用量増加に伴って増加した。増加の程度は 5 倍の用量比よりおおむね大きかった（表 2.6.6-5 参照）。試験期間中，抗ダラツムマブ抗体（ADA）は検出されなかった。詳細な情報は毒性試験概要表【CTD 2.6.7.3 参照】，薬物動態試験の概要文【CTD 2.6.4.3 参照】，薬物動態試験概要表【CTD 2.6.5.1 参照】に記載した。

表 2.6.6-5 チンパンジーを用いたダラツムマブの 6 週間静脈内持続投与及び 13 又は 15 週間回復性試験における血清中曝露量（C_{max} 及び AUC_{0-t}）

投与量 (mg/kg)	群	個体番号	性別	試験計画書の投与日[a]	標準化した投与日[b]	C_{max}[c] (μg/mL)	AUC_{0-t}[c, d] (μg·h/mL)
5[e,f]	1[e,f]	95A015[g]	F	Day 7	0	86	2,799
		96A009	M	Day 7	0	100	2,185
		96A009	M	Day 21	14	129	11,309
		96A009	M	Day 42	35	129	21,450
25[f,h]	2[f,h]	96A015	M	Day 22	0	612	25,885
		96A017	F	Day 22	0	778	39,158
		96A015	M	Day 35	14	630	39,995
		96A017	F	Day 35	14	599	62,112
		96A015	M	Day 56	35	695	146,729
		96A017	F	Day 56	35	967	201,462

a 投与した実際の Day を示す。Day はダラツムマブの 1，3 及び 6 回目投与に対応する。TK 用血液試料を，1，3 及び 6 回目投与の投与前，投与開始 0.58，2，3.5，6.5，24，48 及び 144 又は 168 時間後に採取した。追加血液試料を，第 1 群では最終投与（Day 42）の 96，240，360，528，2016，2184，2352 及び 2520 時間後に，第 2 群では最終投与（Day 56）の 96，240，360，528，1680，1848，2016 及び 2184 時間後に採取した。

b ダラツムマブ投与開始日を Day 0 として標準化した投与日

c 曝露量データ（C_{max} 及び AUC_{0-t}）のみを示す。

d 5 mg/kg 群では，定量可能な最後の TK 試料は，1 及び 3 回目投与では 168 時間後，6 回目投与では 528 時間後に採取された。25 mg/kg 群では，定量可能な最後の TK 試料は，1 回目投与では 144 時間後，3 回目投与では 168 時間後，6 回目投与では 528 時間後に採取された。これらの時点をそれぞれの AUC_{0-t} の算出において「t」とみなした。

e 第 1 群では，Day 0 に溶媒を投与した後，Day 7 にダラツムマブ 5 mg/kg を 30 分間かけて静脈内持続投与した。投与は Day 42 まで週 1 回の頻度で 6 週間行った。

f 投与期間終了後，5 及び 25 mg/kg 群の動物にそれぞれ 15 週間（105 日間）及び 13 週間（91 日間）の休薬期間を置いた。

g 個体番号 95A015 は Day 15 に本薬剤に関係のない事故に遭い投与を中止した。この動物は別の雌チンパンジーに差し替えられたが，その動物（個体番号 92A016）は Day 7 の投与 1.5 時間後に死亡した。個体番号 92A016 の TK 試料は少数［投与前，投与後及び死亡時（投与 1.5 時間後）］しか得られなかったので，そのデータは省いた。

h 第 2 群では，Day 7 に溶媒を投与した。過剰なサイトカイン放出を予防するため，Day 21 にダラツムマブ 10 mg を静脈内にボーラスで前投与し，24 時間後（Day 22）にダラツムマブ 25 mg/kg を 1 時間かけて静脈内持続投与した。以後の静脈内持続投与は 30 分間で行い，前投与は行わなかった。投与は Day 56 まで週 1 回の頻度で 6 週間行った。

【結論】

チンパンジー4 例にダラツムマブを 6 週間静脈内持続投与したとき，全 6 回投与された例数は 4 例中 3 例（5 mg/kg 群の 1 例及び 25 mg/kg 群の 2 例）であった。ダラツムマブの薬理作用に基づく，ヘルパーT 細胞，NK 細胞及び B 細胞の減少／枯渇が観察された。主な毒性所見はサイトカイン放出症候群及び血小板減少症であった。血小板減少症には血中ダラツムマブ濃度の低下とともに回復性が認められた。

ダラツムマブ 25 mg/kg を初回持続投与する 24 時間前に，10 mg を前投与したことにより，サイトカイン放出反応は軽減した。2 回目投与以後，ダラツムマブ 5 及び 25 mg/kg の静脈内持続投与時にはサイトカイン放出症候群は認められなかった。

本試験におけるダラツムマブの NOAEL は 5 mg/kg 未満と判定された。

2.6.6.4 遺伝毒性試験

ダラツムマブの遺伝毒性試験は実施しなかった。ICH S6(R1)ガイドラインに基づき，従来の医薬品について実施されてきた遺伝毒性試験は，バイオ医薬品に対しては適切なものでなく必要とされていない。ダラツムマブは分子量が約 148 kDa の mAb であることから，細胞内に移行して DNA と直接，相互作用することはなく，生体内で産生される免疫グロブリンと同様に代謝される。

2.6.6.5 がん原性試験

ダラツムマブのがん原性試験は実施しなかった。ICH S9 ガイドラインに基づき，再発又は難治性の多発性骨髄腫（MM）などの進行がんの患者の治療を目的とした医薬品の製造販売承認申請には，がん原性試験は必要とされていない。

さらに，ICH S6(R1)ガイドラインに基づき，げっ歯類の動物と交差反応を示さないバイオ医薬品の場合，げっ歯類を用いた標準的ながん原性試験は一般的に不適切である。

2.6.6.6 生殖発生毒性試験

進行がん患者の治療を目的とした医薬品の製造販売承認申請時には，受胎能，初期胚発生，並びに出生前及び出生後の発生に関する試験は必須ではない（ICH S9 ガイドライン）。しかし，胚・胎児発生の評価については通常実施される。前述したとおり，チンパンジーは薬理学的に毒性評価に適した唯一の動物種であるが，絶滅危惧種であるチンパンジーを用いて生殖発生毒性試験を実施することは不可能である。カニクイザルにサロゲート抗体を投与することも考慮したが，この動物種を用いて生殖発生毒性試験を追加実施した場合，貧血及び ADA 産生により用量及び投与期間が制限されることが考えられたことから，生殖発生毒性試験は実施しなかった。

2.6.6.7 局所刺激性試験

ダラツムマブの局所刺激性を評価するための特別な試験は実施しなかった。臨床投与経路である静脈内投与時の注射部位反応は，カニクイザル及びチンパンジーを用いた反復投与毒性試験の一環として，剖検及び病理組織学的検査で評価した。静脈内持続投与後に認められた注射部位反応は，静脈穿刺に伴って通常みられるような変化であった。

2.6.6.8 その他の毒性試験

HuMab-CD38（カニクイザルの CD38 に結合する mAb）及びダラツムマブの抗原性，免疫毒性に関する評価はそれぞれ，カニクイザル及びチンパンジーを用いた反復投与毒性試験の試験デザインに組み入れた【CTD 2.6.6.3.1 及び 2.6.6.3.2 参照】。

チンパンジー正常組織及びヒト正常組織へのダラツムマブの結合性を評価するために，フルオレセインイソチオシアネート（FITC）標識ダラツムマブを用いて IHC 解析による組織交差反応性試験を実施した。

2.6.6.8.1 抗原性試験

HuMab-CD38 及びダラツムマブに対する ADA 産生を，それぞれカニクイザル及びチンパンジーを用いた反復投与毒性試験の中で評価した。カニクイザルでは 20 mg/kg 投与群（回復試験群）の 2 例から HuMab-CD38 に対する ADA が検出された。100 mg/kg 投与群では ADA 反応はみられなかったが，その理由として血清中に存在する高濃度の HuMab-CD38 が抗体検出に干渉した可能性が考えられる。一方，チンパンジーからは ADA は検出されなかった。

なお，毒性試験における ADA の産生から，ヒトにおける免疫原性の可能性を予測することは困難である [1)] 。

2.6.6.8.2 免疫毒性試験

カニクイザル及びチンパンジーを用いた反復投与毒性試験の中で，免疫毒性について評価した。

2.6.6.8.3 依存性試験

神経伝達物質又はその受容体とダラツムマブの作用機序との間に相互関係はないことから，乱用の可能性は予測されず，したがって，薬物乱用に関する非臨床試験は実施しなかった。

2.6.6.8.4 代謝物の毒性試験

mAb については代謝物を用いた毒性試験は求められていない［ICH S6(R1)ガイドライン参照］ことから，ダラツムマブの代謝物を用いた毒性試験は実施していない。ダラツムマブは代謝によって低分子ペプチド及び個々のアミノ酸に分解されると考えられている。これらの代謝経路は広く理解されており，アミノ酸は本薬物とは関係のないタンパク質又はペプチドに再利用される。

2.6.6.8.5 不純物の毒性試験

ダラツムマブに関連する不純物の毒性試験は実施しなかった。ダラツムマブの製造法には不純物及び混入物を除去する精製工程に加え，製品の生物学的分析による厳密な特性解析が含まれている。ダラツムマブ製剤中に毒性試験を実施する必要がある不純物は含まれていない。

2.6.6.8.6 新添加物の毒性試験

本製剤中には，新添加物に該当する化合物又は使用実績を超える量の添加物は含まれていない。

2.6.6.8.7 組織交差反応性試験

FITC 標識 HuMab-CD38 とカニクイザル正常組織試料を用いた組織交差反応性試験を実施した。また，FITC 標識ダラツムマブとチンパンジー及びヒトの正常組織を用いた組織交差反応性試験も実施した。ダラツムマブとの特異的結合が認められた組織は，ほとんどがリンパ系組織であった。いずれの種でもダラツムマブとの結合が複数組織の細胞質で認められたが，mAb は細胞内に移行しないことから，細胞質に認められた mAb 結合に毒性学的及び臨床的意義はない。

2.6.6.8.7.1 FITC 標識 HuMab-CD38 とカニクイザル正常組織との組織交差反応性試験

【評価資料 4.2.3.7.7.1】

【試験方法】

本試験の目的は，カニクイザルの CD38 に結合する FITC 標識 HuMab-CD38 の組織結合特異性を，カニクイザル 3 例から得た 35 種類の正常組織を用いて決定することにあった。

検討した組織は，副腎，脳（小脳及び大脳），乳房，眼（網膜を含む），卵管，消化管（胃，小腸及び大腸），心臓，腎臓，肝臓，肺，リンパ節，卵巣，膵臓，末梢神経，下垂体，前立腺，耳下腺，皮膚，脊髄，脾臓，横紋筋，精巣，胸腺，甲状腺及び副甲状腺，扁桃，膀胱，尿管，子宮（子宮頚部及び子宮内膜），並びに血管内皮であった。血液学的検査用試料（血液細胞及び骨髄）から作製したスメア又はサイトスピン標本についても評価した。本試験で使用されたすべての組織は，試験に供与する前にヘマトキシリン - エオジン又はギムザ（血液及び骨髄の場合）及び適切な抗原マーカーによって染色を行った。

本試験では，二次抗体［西洋ワサビペルオキシダーゼ（HRP）標識ウサギ抗 FITC 抗体］及び三次抗体（ビオチン化標識ブタ抗ヤギ／マウス／ウサギ IgG）を用いて 3 ステップの間接法［ストレプトアビジン-ビオチン-西洋ワサビペルオキシダーゼ複合体（ABC）法］で実施した。FITC 標識ヒト IgG を陰性対照抗体として用いた。陽性対照及び陰性対照組織として，それぞれカニクイザル胸腺及び皮膚を用いた。各組織試料のアセトン固定凍結切片を 0，0.2，0.5 及び 1 μg/mL の濃度の FITC 標識 HuMab-CD38 で処理した。

【結果】

陽性対照及び陰性対照の試験結果から試験系の妥当性が示された。

染色は血管，骨髄リンパ球，小脳白質，大脳白質，子宮頸部，結腸粘膜固有層，卵管間質，回腸粘膜固有層，肺胞細胞，リンパ節 T 細胞，末梢神経ミエリン，網膜／脈絡膜硝子膜，脊髄白質，脾臓 T 細胞域，胃，横紋筋線維，胸腺髄質及び皮質中の T 細胞，扁桃 T 細胞域の細胞質内で観察された。細胞質が特に薄い内皮（毛細血管）細胞，並びに腎臓糸球体間質又は肝臓類洞内では，特異的染色の細胞内位置を決定することはできなかった。腎臓及び肝臓では，間質／類洞中の染色が内皮細胞の染色を示している可能性が考えられた。

2.6.6.8.7.2　FITC 標識ダラツムマブとチンパンジー正常組織との組織交差反応性試験

【評価資料 4.2.3.7.7.2】

【試験方法】

本試験の目的は，チンパンジーの正常組織標本を用いて FITC 標識ダラツムマブの組織結合特異性を決定することであった。評価したチンパンジーの組織（1～2 例/1～2 組織試料）は副腎，骨髄，脳，結腸，内皮（心臓），卵管，消化管（小腸），心臓，腎臓（糸球体及び尿細管），肝臓，肺（細気管支及び肺胞），リンパ節（腸間膜リンパ節を含む），膵臓，下垂体，皮膚，脊髄，脾臓，横紋筋，扁桃及び精巣であった。

アセトン固定凍結切片を 0.25 及び 1.25 μg/mL の濃度の FITC 標識ダラツムマブで処理し，結合した抗体をビオチン化ヤギ抗フルオレセイン二次抗体で検出した。結合した複合体を，ABC 法及び基質発色剤ジアミノベンジジンで可視化した。

CD38 陽性細胞を含むヒトリンパ節試料を陽性対照として用い，CD38 陽性細胞をほとんど又は全く含まないヒト膀胱組織試料を陰性対照として用いた。FITC 標識ヒト IgG を陰性対照抗体として用いた。抗 CD31 抗体（血小板内皮細胞接着分子 PECAM-1 に対する抗体）を用いて染色することにより，組織試料に関する IHC 解析の妥当性が確認された。

【結果】

陽性対照では特異的結合が観察された。陰性対照組織では，いずれの濃度でも，粘膜中及び粘膜下の少数の散在した細胞に軽微な染色が認められたが，これらの細胞は CD38 陽性と予想される単核球系炎症細胞である可能性が考えられた。陰性対照抗体を用いて染色した連続切片には特異的結合は認められなかった。

ダラツムマブ-FITC による特異的染色は，リンパ系細胞及びマクロファージ，並びに脾臓，扁桃，リンパ節及び腸管粘膜固有層中の造血細胞で認められた。特異的結合は複数のチンパンジー組織（副腎，骨髄，脳，結腸，卵管，消化管，心臓，腎臓，肝臓，リンパ節，腸間膜リンパ節，膵臓，下垂体，皮膚，脊髄，脾臓，横紋筋，精巣及び扁桃）の細胞質内でも検出された。肺のみ特異的結合が認められなかった。

2.6.6.8.7.3　FITC 標識ダラツムマブとヒト正常組織との組織交差反応性試験

【評価資料 4.2.3.7.7.3】

【試験方法】

本試験の目的は，ヒト成人正常組織試料（37 種類の組織；3 例のドナー由来）を用いて FITC 標識ダラツムマブの組織結合特異性を決定することにあった。使用した組織は，欧州医薬品庁のガイドライン「Production and Quality Control of Monoclonal Antibodies」[2)] の Annex II に示されている「suggested list of human tissues to be used for immunohistochemical investigations of cross reactivity（交差反応性の免疫組織化学的検討において使用すべきヒト組織の一覧）」，及び FDA／生物学的製剤評価研究センターの「Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use」[3)] で推奨されている組織に基づいた。本試験で使用されたすべての組織は，試験に供与する前にヘマトキシリン‐エオジン又はギムザ（血液及び骨髄の場合）及び適切な抗原マーカーによる染色を行った。

本試験では，二次抗体（HRP 標識ウサギ抗 FITC 抗体）及び三次抗体（ビオチン化ブタ抗ヤギ／マウス／ウサギ IgG）を用いて 3 ステップの間接法（ABC 法）で実施した。FITC 標識ヒト IgG を陰性対照抗体として用いた。陽性対照及び陰性対照組織として，それぞれヒト扁桃及びヒト皮膚を用いた。各組織試料の切片を 0，0.5，1 及び 2 μg/mL の濃度の FITC 標識ダラツムマブで処理した。

【結果】

陽性対照及び陰性対照の試験結果から試験系の妥当性が示された。

ダラツムマブ-FITC による特異的染色は，脾臓，扁桃，リンパ節及び胸腺のリンパ系細胞で認められた。ダラツムマブの特異的結合は，複数のヒト組織（下垂体の毛細血管，卵管の血管内皮細胞，回腸漿膜，副甲状腺，リンパ節，脾臓，胸腺及び扁桃中のリンパ球，腎臓，精巣及び甲状腺の間質細胞，卵管の上皮細胞並びに前立腺）の細胞質内でも検出された。下垂体及び卵管の血管内皮における染色の細胞内位置を決定することはできなかった。

2.6.6.9 考察及び結論

ダラツムマブは，骨髄腫，リンパ腫，白血病等の血液悪性腫瘍においては高レベルで，またその他の種類の細胞や組織においては種々のレベルで発現している CD38 と特異的に結合する免疫グロブリン G1κ（IgG1κ）ヒトモノクローナル抗体である【CTD 2.6.2.2.3.1 参照】。

MM は CD38 を高レベルで発現していることから，CD38 を標的とする治療法は MM の患者に，CD38 を低レベルで発現している正常組織を傷つけることなく有益な作用をもたらすと考えられる。

ダラツムマブは，チンパンジー及びヒトの CD38 に結合するが，マウス，ラット，ウサギ，ブタ，カニクイザル及びアカゲザルなど毒性試験において一般的に用いられる動物種の CD38 には結合しない。したがって，ダラツムマブの主要な毒性試験は，チンパンジーを用いた反復投与毒性試験，並びにチンパンジー及びヒトの正常組織を用いた組織交差反応性試験のみとした。

毒性試験にはダラツムマブ及び HuMab-CD38 を使用した。HuMab-CD38 はカニクイザルの CD38 と高い親和性で結合し，ダラツムマブで観察されるのと同程度の ADCC を誘導する。しかし，HuMab-CD38 は，ヒト腫瘍細胞に対する *in vitro* CDC 作用がダラツムマブより弱く，ヒト CD38 のシクラーゼ活性を阻害しない。

HuMab-CD38 については，カニクイザルを用いた反復投与毒性試験及びカニクイザル正常組織を用いた組織交差反応性試験を実施した。HuMab-CD38 を 1 週間隔で 2 回投与したとき，カニクイザルは貧血及び免疫原性を発現した。ダラツムマブと HuMab-CD38 の作用機序が異なること，ヒトとカニクイザルでは CD38 の生物学的特性が異なること（HuMab-CD38 とカニクイザルの RBC との結合はダラツムマブとヒトの RBC との結合よりもはるかに強い）及び貧血が認められたことから，カニクイザルを用いた追加試験を実施する科学的価値及び妥当性は低いと判断した。

チンパンジーを用いた 6 週間反復投与毒性試験には急性毒性，局所刺激性及び安全性薬理試験の評価項目を組み入れた。ダラツムマブはがんを適応症とする mAb であることから遺伝毒性試験，がん原性試験及び生殖発生毒性試験は，ICH S6(R1)及び ICH S9 ガイドラインに基づき実施しなかった。

主な毒性所見はサイトカイン放出反応と血小板減少症であった。サイトカイン放出反応はダラツムマブ初回投与時に認められたが，2 回目以後の投与時には発現しなかった。低用量（5 mg/kg）群の 1 例が初回投与後に死亡した。そのため高用量（25 mg/kg）群においてサイトカインの過剰放出反応が生じるのを予防するため，ダラツムマブ 25 mg/kg を初回持続投与する 24 時間前に，ダラツムマブ 10 mg を静脈内に前投与した。この処置によって，25 mg/kg 群では初回持続投与後のサイトカイン放出反応が軽減された。サイトカイン放出反応は臨床では IRR に相当すると考えられ，本剤の臨床試験では被験者に対して副腎皮質ステロイド，解熱鎮痛剤及び抗ヒスタミン剤の前投薬を行うとともに，本剤の投与調節を行うことにより，ほとんどの IRR は臨床的に管理可能であった【CTD 2.7.4.2.1.5 (1)参照】。チンパンジーにおける血小板減少症は，血液中からダラツムマブが消失するに伴い回復した。ヒトとチンパンジーの血小板に対するダラツムマブの結合には種差が認められた【CTD 2.6.2.3.2 参照】。ダラツムマブの薬理作用に基づく，ヘルパーT 細胞，NK 細胞及び B 細胞の減少が観察された。チンパンジーは絶滅危惧種であることから，屠殺して検査を行うことは許容されないため，剖検，器官重量及び病理組織学的検査のデータは得られない。海外規制当局は，チンパンジーが薬理学的に毒性評価に適した唯一の動物種であることから，本適応症取得のためにこれ以上反復投与毒性試験を実施する必要はないことに合意している（[redacted]年[redacted]月[redacted]日の FDA との IND 前相談議事録，又は EMA の [redacted]年[redacted]月[redacted]日付科学的助言）。

2.6.6.10 図表

図表は本文中に記載した。

2.6.6.11 参考文献

1） Bugelski PJ, Treacy G. Predictive power of preclinical studies in animals for the immunogenicity of recombinant therapeutic proteins in humans. Curr Opin Mol Ther. 2004;6(1):10-6.

2） European Medicines Agency Guideline. Production and Quality Control of Monoclonal Antibodies. Directive 75/318/EEC. 1995. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003444.pdf

3） U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use. 1997. http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/UCM153182.pdf.

2.6.7 毒性試験概要表

2.6.7.1 毒性試験

一覧表

Test Article: Daratumumab [a]

Type of Study	Species and Strain	Route (Vehicle/Formulation)	Duration of Dosing	Doses (mg/kg) [b]	Compounds/ Batch No.	TK	ADA	GLP	Testing Facility	Study No. Location in CTD
Single-Dose Toxicity	NA									
Repeat-Dose Toxicity	Cynomolgus Monkey	IV (30 min. infusion) (Vehicle: 12.6 mmol/L sodium phosphate and 140 mmol/L sodium chloride, pH 7.4;HuMab-CD38 [c]: 11.16 mg/mL in 12.6 mmol/L sodium phosphate and 140 mmol/L sodium chloride, pH 7.2-7.4)	2 weeks weekly (+ 2 months recovery) [d]	0, 20, 100	HuMab-CD38 [c] / [redacted]	Yes	Yes	No	[redacted] UK	509809 4.2.3.2.1
	Chimpanzee	IV (30 min. infusion) [e] IV (1 h infusion) [f] (Vehicle: 25 mmol/L sodium acetate, 60 mmol/L sodium chloride, 140 mmol/L mannitol, 0.006% polysorbate 20, pH 5.5; Daratumumab: 21.1 mg/mL in Sterile pyrogen free 0.9% NaCl 125 mL dilution).	6 weeks weekly (+ 91 or 105 day recovery) [g]	0→5 [e] 0→25 [f]	Daratumumab (HuMax-CD38) [h]/ [redacted]	Yes	Yes	Yes	[redacted]	8754-0701 4.2.3.2.2

[a] Studies were conducted with daratumumab unless otherwise specified.
[b] Unless otherwise specified. For Repeat-Dose Toxicity, the highest NOAEL (No Observed Adverse-Effect Level) is underlined where available. A NOAEL was not determined for these studies.
[c] The supportive study was conducted with HuMab-CD38, a human IgG1 mAb that specifically binds to human and cynomolgus monkey CD38.
[d] Animals were dosed on Days 1 and 8. Animals from the main study group (1/sex/group) were euthanized on Day 11, and animals from the recovery group (1/sex/group) were allowed to recover for 56 days, then euthanized on Day 64.
[e] Animals assigned to Group 1 were administered the vehicle on Day 0, followed by a 5 mg/kg IV infusion (30 min.) of daratumumab on Day 7; dosing occurred weekly for 6 weeks until Day 42.
[f] Animals assigned to Group 2 were administered the vehicle on Day 7. In order to prevent exaggerated cytokine release, animals received a 10 mg pre-dose of daratumumab via IV injection on Day 21, followed by a 25 mg/kg IV infusion (1 h) of daratumumab administered 24 h later on Day 22; infusion (30 min.) occurred weekly for 6 weeks until Day 56.
[g] The treatment period was followed initially by a 56 day (ie, 2-month) recovery period; the recovery period was subsequently extended up to a total of 105 or 91 days for low (5 mg/kg) and high (25 mg/kg) dose animals, respectively.
[h] The study was conducted with daratumumab (ie, HuMax-CD38), a human IgG1 mAb that specifically binds to human and chimpanzee CD38.

ADA = anti-drug antibodies; GLP = Good Laboratory Practice; h = hour; HuMax-CD38 = daratumumab; HuMab-CD38 = anti-cynomolgus CD38 mAb; IgG = immunoglobulin G; IV = intravenous; mAb = monoclonal antibody; min. = minute; NA = not applicable; TK = toxicokinetics

(Continued)

2.6.7.1 毒性試験

一覧表（続き）

Test Article: Daratumumab [a]

Type of Study	Species and Strain	Route (Vehicle/Formulation)	Duration of Dosing	Doses (µg/mL) [a]	Compounds/ Batch No.	TK	ADA	GLP	Testing Facility	Study No. Location in CTD
Genotoxicity				NA						
Carcinogenicity				NA						
Reproductive and Developmental Toxicity				NA						
Local Tolerance				NA						
Other Toxicity Studies Tissue Cross-Reactivity	Normal cynomolgus monkey tissues	*In vitro*	NA	0, 0.2, 0.5, 1	HuMab-CD38 [c]/ [redacted]	No	No	Yes	[redacted] UK	510547 4.2.3.7.7.1
	Normal chimpanzee tissues	*In vitro*	NA	0.25, 1.25	Daratumumab (HuMax-CD38)[b]/ [redacted]	No	No	Yes	[redacted]	BKV 00003 4.2.3.7.7.2
	Normal human tissues	*In vitro*	NA	0, 0.5, 1, 2	Daratumumab (HuMax-CD38) [c]/ [redacted]	No	No	Yes	[redacted] UK	260571 4.2.3.7.7.3

[a] Studies were conducted with daratumumab unless otherwise specified.
[b] Studies were conducted with daratumumab conjugated to FITC. Daratumumab is a human IgG1 mAb that specifically binds to human and chimpanzee CD38.
[c] The study was conducted with HuMab-CD38 conjugated to FITC. HuMab-CD38 is a human IgG1 mAb that specifically binds to human and cynomolgus monkey CD38.

ADA = anti-drug antibodies; FITC = fluorescein isothiocyanate; GLP = Good Laboratory Practice; HuMax-CD38 = daratumumab; HuMab-CD38 = anti-cynomolgus CD38 mAb; IgG = immunoglobulin G; mAb = monoclonal antibody; NA = not applicable; TK = toxicokinetics

2.6.7.2 トキシコキネティクス

トキシコキネティクス試験の一覧表

Test Article: Daratumumab [a]

Type of Study	Test System	Route (Vehicle/Formulation)	Doses (mg/kg)	GLP	Study No. Location in CTD
Repeat-Dose Toxicity [2 weeks (weekly) + 2 months recovery] [b]	Cynomolgus Monkey	IV (30 min. infusion) Vehicle: 12.6 mmol/L sodium phosphate and 140 mmol/L sodium chloride, pH 7.4; HuMab-CD38 [c]: 11.16 mg/mL in 12.6 mmol/L sodium phosphate and 140 mmol/L sodium chloride, pH 7.2-7.4	0, 20, 100 [c]	No	509809 4.2.3.2.1
Repeat-Dose Toxicity [6 weeks (weekly) + 91 or 105 days recovery] [d]	Chimpanzee	IV (30 min. infusion) [e] IV (1 h infusion) [f] Vehicle: 25 mmol/L sodium acetate, 60 mmol/L sodium chloride, 140 mmol/L mannitol, 0.006% polysorbate 20, pH 5.5; Daratumumab (HuMax-CD38) [g]: 21.1 mg/mL in sterile pyrogen free 0.9% NaCl 125 mL dilution	0→5 [e,g] 0→25 [f,g]	Yes	8754-0701 4.2.3.2.2

[a] Studies were conducted with daratumumab unless otherwise specified.
[b] Animals were dosed on Days 1 and 8. Animals from the main study group (1/sex/group) were euthanized on Day 11, and animals from the recovery group (1/sex/group) were allowed to recover for 56 days, then euthanized on Day 64.
[c] The study was conducted with HuMab-CD38, a human IgG1 mAb that specifically binds to human and cynomolgus monkey CD38.
[d] The treatment period was followed initially by a 56 day (ie, 2-month) recovery period; the recovery period was subsequently extended up to a total of 105 or 91 days for low (5 mg/kg) and high (25 mg/kg) dose animals, respectively.
[e] Animals assigned to Group 1 were administered the vehicle on Day 0, followed by a 5 mg/kg IV infusion (30 min.) of daratumumab on Day 7; dosing occurred weekly for 6 weeks until Day 42.
[f] Animals assigned to Group 2 were administered the vehicle on Day 7. In order to prevent exaggerated cytokine release, animals received a 10 mg pre-dose of daratumumab via IV injection on Day 21, followed by a 25 mg/kg IV infusion (1 h) of daratumumab administered 24 h later on Day 22; infusion (30 min.) occurred weekly for 6 weeks until Day 56.
[g] The study was conducted with daratumumab, a human IgG1 mAb that specifically binds to human and chimpanzee CD38

h = hour; HuMab-CD38 = anti-cynomolgus CD38 mAb; IgG = immunoglobulin G; IV = intravenous; mAb = monoclonal antibody; min. = minute

2.6.7.3 トキシコキネティクス

トキシコキネティクス試験成績の一覧表

C_{max}（μg/mL）及び AUC_{0-t}（μg·h/mL）

Test Article: HuMab-CD38 [a]

Cynomolgus Monkey
（Mod 4.2.3.2.1/509809）

Dose (mg/kg) [b]	Group	Animal ID	Dosing Day	C_{max} (μg/mL)	AUC_{0-t} [c] (μg·h/mL)
20	2 (Main)	3M	1	1920.0	35,452.6
	2 (Recovery)	4M [d]		682.0	29,122.4
	2 (Main)	9F		416.0	21,807.9
	2 (Recovery)	10F [d]		498.0	33,319.3
	2 (Main)	3M	8	707.0	19,698.1
	2 (Recovery)	4M [d]		815.0	43,435.5
	2 (Main)	9F		481.0	14,784.9
	2 (Recovery)	10F [d]		558.0	32,000.9
100	3 (Main)	5M	1	2880.0	138,086.5
	3 (Recovery)	6M		3760.0	237,890.0
	3 (Main)	11F		2880.0	196,521.5
	3 (Recovery)	12F		3980.0	189,266.5
	3 (Main)	5M	8	3810.0	101,670.8
	3 (Recovery)	6M		3460.0	403,617.4
	3 (Main)	11F		3880.0	110,092.3
	3 (Recovery)	12F		3820.0	703,593.1

[a] Animals were administered HuMab-CD38, a human IgG1 mAb that specifically binds to human and cynomolgus monkey CD38.

[b] Animals (2/sex/group) were administered HuMab-CD38 weekly via IV infusion for 2 weeks (ie, with dosing on Days 1 and 8). Only exposure data is provided here; refer to Mod2.6.4, the Nonclinical Pharmacokinetics Written Summary and to Nonclinical Pharmacokinetics Tabulated Summary 2.6.5.4B for information on additional TK parameters.

[c] Blood samples were collected for serum TK analysis on Day 1 at the following time points: prior to, immediately after, and 0.5, 1.5, 3, 6, 12, 24, 48, 72, and 120 h after the first infusion; blood samples were also collected prior to infusion on Day 8. On Day 8, blood samples were collected from the main study group animals for serum TK analysis immediately after, and 0.5, 1.5, 3, 6, 12, 24 and 48h after infusion. Blood samples were collected on Day 8 from the recovery animals at the following time points: immediately after, and 0.5, 1.5, 3, 6, 12, 24, 48, 72, and 120 h after infusion; samples were also obtained on Days 15, 18, 21, 24, 28, 32, 36, 40, 50, and 64. Values shown are for AUC_{0-t}.

[d] Recovery animals 4M and 10F from the 20 mg/kg dose group were considered to exhibit a positive antibody response (defined as a greater than 4-fold increase over the initial titre) towards the end of the study on Days 21, 36, 50 and 64 (No. 4M), and on Days 21, 36, and 64 (No. 10F), respectively; their individual values for Days 1 and 8 are provided here.

F = female; h = hour; HuMab-CD38 = anti-cynomolgus CD38 mAb; IgG = immunoglobulin G; IV = intravenous; M = male; mAb = monoclonal antibody; No. = number; TK = toxicokinetics

(Continued)

2.6.7.3 トキシコキネティクス

トキシコキネティクス試験成績の一覧表（続き）

C_{max}（μg/mL）及び AUC_{0-t}（μg·h/mL）

Test Article: Daratumumab [a]

Chimpanzee (Mod4.2.3.2.2/8754-0701)							
Dose (mg/kg)	**Group**	**Animal No.**	**Sex**	**Study Day** [b]	**Dosing Day** [c]	**C_{max} (μg/mL)**	**AUC_{0-t}** [d] **(μg·h/mL)**
5 [e,f]	1 [e,f]	95A015 [g]	F	7	0	86	2,799
		96A009	M	7	0	100	2,185
		96A009	M	21	14	129	11,309
		96A009	M	42	35	129	21,450
25 [f,h]	2 [f,h]	96A015	M	22	0	612	25,885
		96A017	F	22	0	778	39,158
		96A015	M	35	14	630	39,995
		96A017	F	35	14	599	62,112
		96A015	M	56	35	695	146,729
		96A017	F	56	35	967	201,462

[a] Animals were administered daratumumab unless otherwise noted. Only exposure data is provided here; refer to Mod2.6.4, the Nonclinical Pharmacokinetics Written Summary and to Nonclinical Pharmacokinetics Tabulated Summary 2.6.5.4A for information on additional TK parameters.

[b] Actual Study Day of dosing shown. Days correspond to the first, third, and sixth administrations. Blood samples were collected for serum TK analysis prior to infusion and 0.58, 2, 3.5, 6.5, 24, 48, and 144 or 168 h after the initiation of the first, third, and sixth doses. Additional blood samples were collected after the sixth infusion in Group 1 (96, 240, 360, 528, 2016, 2184, 2352, and 2520 h) and Group 2 (96, 240, 360, 528, 1680, 1848, 2016, and 2184 h).

[c] Standardized dosing days relative to start of daratumumab administration.

[d] In the 5 mg/kg cohort, the last quantifiable TK sample was collected 168 h after the first and third dose, and 528 h after the sixth dose. In the 25 mg/kg cohort, the last quantifiable TK sample was collected 144 h after the first dose, 168 h after the third dose, and 528 h after the sixth dose. These time points were considered "t" for the respective calculations of AUC_{0-t}.

[e] Animals from Group 1 (1/sex) were administered the vehicle on Study Day 0, followed by a 5 mg/kg IV infusion (30 min.) of daratumumab on Study Day 7; dosing occurred weekly for 6 weeks until Study Day 42.

[f] The treatment period was followed by a 105 or 91 day recovery period for low (5 mg/kg) and high (25 mg/kg) dose animals, respectively.

[g] On Study Day 15, female No. 95A015 had a non-drug-related accident and treatment was discontinued. She was replaced by another female chimpanzee; that replacement animal (No. 92A016), however, died 1.5 h after the Study Day 7 infusion. As only limited TK samples (pre-dose, post-dose, and terminal [ie, 1.5 h post-dose]) were obtained for No. 92A016, data for that animal are not provided here.

[h] Animals assigned to Group 2 (1/sex) were administered the vehicle on Study Day 7. In order to prevent exaggerated cytokine release, animals received a 10 mg pre-dose of daratumumab via IV injection on Study Day 21, followed by a 25 mg/kg IV infusion (1 h) of daratumumab administered 24 h later on Study Day 22; infusion (30 min.) occurred weekly for 6 weeks until Study Day 56.

F = female; h = hour; IV = intravenous; M = male; min. = minute; No. = number; TK = toxicokinetics

2.6.7.4 毒性試験

被験物質の一覧表 **Test Article**: Daratumumab

Compound	Batch No.	Purity (%)	Endotoxin (EU/mg)	Type of Study	Study No./ Location in CTD
Proposed Specification:		≥90.0			
Daratumumab [a] (HuMax-CD38)	[redacted]	>99.0 [b]	0.004	Daratumumab: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period	8754-0701 4.2.3.2.2
	[redacted]	Comparable to starting material prior to labeling [c]	NA [d]	Tissue Cross-Reactivity of FITC-Labeled Daratumumab with Chimpanzee Tissues Ex Vivo	BKV00003 4.2.3.7.7.2
				Daratumumab-FITC: An Immunohistochemical Investigation of Cross-Reactivity in a Range of Human Tissues	260571 4.2.3.7.7.3
HuMab-CD38	[redacted]	>99.0 [b]	1.4	HuMab-CD38 ([redacted]): Pilot Toxicology and Pharmacokinetic Study in Cynomolgus Monkeys with a Two Month Recovery Period	509809 4.2.3.2.1
	[redacted]	Comparable to [redacted] [c]	NA [d]	HuMab-CD38-FITC: An Immunohistochemical Investigation of Cross-Reactivity in a Range of Cynomolgus Monkey Tissues	510547 4.2.3.7.7.1

[a] Studies were conducted with daratumumab unless otherwise specified. Information on the compound used is provided in the first column in parentheses.
[b] Purity by HP-SEC.
[c] Purity by non-reducing SDS-PAGE.
[d] Endotoxins not measured for FITC labeled material.

FITC = fluorescein isothiocyanate; HuMab-CD38 = anti-cynomolgus CD38 mAb; mAb = monoclonal antibody; NA = not applicable

2.6.7.5 単回投与毒性試験

該当資料なし

2.6.7.6 反復投与毒性試験：重要な試験以外の試験

Test Article: HuMab-CD38 [a]

Report Title: HuMab-CD38 ([redacted]): Pilot Toxicology and Pharmacokinetic Study in Cynomolgus Monkeys with a Two Month Recovery Period

Species/Strain: Monkey/Cynomolgus
Duration of Dosing: 2-weeks (weekly; Days 1 and 8) [b]
Study No.: 509809
Age at First Dose: 14-21 months
Duration of Postdose Recovery: 56 days (1/sex/group) [b]
Location in CTD: 4.2.3.2.1
Date of First Dose: [redacted], [redacted]
Route: IV infusion (30 min.)
GLP Compliance: No

Vehicle/Formulation: Vehicle: 12.6 mmol/L sodium phosphate and 140 mmol/L sodium chloride, pH 7.4; HuMab-CD38: 11.16 mg/mL in 12.6 mmol/L sodium phosphate and 140 mmol/L sodium chloride, pH 7.2-7.4

Special Features: Physical examinations (pre-study, once daily Days 1 to 9, weekly thereafter); ophthalmoscopic examinations (pre-study, Days 10, 30 and 52); body temperatures (weekly Days -7 to 56); ECGs and heart rates (pre-study, Days 1 and 8); TDAR (anti-KLH analysis; Days 1, 8, 11, 15, 22, 29, 36, 43, 50, 55, 58, 61 and 64) [c]; Coombs test (Days 8, 28 and 64); flow cytometry for immunophenotyping of peripheral blood subsets (pre-study, Days 1, 8, 11, 15, 21, 28, 36, 50 and 64); flow cytometry and IHC of biopsies of superficial lymph nodes (pre-study, Days 7, 21, 35, 50, and necropsy Days 11 and 64). IHC performed on select tissues for determination of the proportion of CD38 positive lymphocytes binding HuMab-CD38 and CD38 positive lymphocytes with receptors for HuMab-CD38. Serum TK and ADA were measured.

No Observed Adverse Effect Level: NA [d]

DOSING AND RECOVERY PERIOD

Dose (mg/kg/week)	**0 (Control)**				**20**				**100**			
No. of Animals	M:2		F:2		M:2		F:2		M:2		F:2	
Toxicokinetics:												
No. of Animals	M:2		F:2		M:2		F:2		M:2		F:2	
Animal ID No.	1M [e]	2M [f]	7F [e]	8F [f]	3M [e]	4M [f,g]	9F [e]	10F [f,g]	5M [e]	6M [f]	11F [e]	12F [f]
AUC (µg·h/mL) [h]												
Day 1					35,452.6	29,122.4	21,807.9	33,319.3	138,086.5	237,890.0	196,521.5	189,266.5
Day 8					19,698.1	43,435.5	14,784.9	32,000.9	101,670.8	403,617.4	110,092.3	703,593.1
C_{max} (µg/mL) [h]												
Day 1					1920.0	682.0	416.0	498.0	2,880.0	3,760.0	2,880.0	3,980.0
Day 8					707.0	815.0	481.0	558.0	3,810.0	3,460.0	3,880.0	3,820.0
ADA titre (1:×) [g]												
Pre-dose (Day -7)						<50		<50				
Day 8						<50		100				
Day 15						<50		100				
Day 21						400		800				
Day 28						<50		100				
Day 36						800		800				
Day 50						400		<50				
Day 64						1600		1600				

(Continued)

2.6.7.6 反復投与毒性試験：重要な試験以外の試験（続き）

Test Article: HuMab-CD38 [a]

Report Title: HuMab-CD38 ([redacted]): Pilot Toxicology and Pharmacokinetic Study in Cynomolgus Monkeys with a Two Month Recovery Period

[a] The study was conducted with HuMab-CD38, a human IgG1 mAb that specifically binds to human and cynomolgus monkey CD38.
[b] Animals were dosed on Days 1 and 8. Animals from the main study group (1/sex/group) were euthanized on Day 11, and animals from the recovery group (1/sex/group) were allowed to recover for 56 days, then euthanized on Day 64.
[c] Monkeys received a SC injection of KLH in FIA at 0.5 mg on Day -7 and at 0.3 mg on Days 1, 8, and 55; humoral immune function (ie, TDAR) was assessed by assay of serum IgM and IgG titers from blood samples collected during the treatment and recovery phases.
[d] A NOAEL was not reached during the study.
[e] Animals assigned to the main study group.
[f] Animals assigned to the recovery study group.
[g] Recovery animals 4M and 10F from the 20 mg/kg dose group were considered to exhibit a positive antibody response (defined as a greater than 4-fold increase over the initial titre) towards the end of the study on Days 21, 36, 50 and 64 (No. 4M), and on Days 21, 36, and 64 (No. 10F), respectively. Information on ADA titre (ie, the endpoint titre obtained, presented as 1:×, where × represents the dilution) is shown only for the 2 animals that were ADA positive.
[h] Blood samples were collected for serum TK analysis on Day 1 at the following time points: prior to, immediately after, and 0.5, 1.5, 3, 6, 12, 24, 48, 72, and 120 h after the first infusion; blood samples were also collected prior to infusion on Day 8. On Day 8, blood samples were collected from the main study group animals for serum TK analysis immediately after, and 0.5, 1.5, 3, 6, 12, 24 and 48 h after infusion. Blood samples were collected on Day 8 from the recovery animals at the following time points: immediately after, and 0.5, 1.5, 3, 6, 12, 24, 48, 72, and 120 h after infusion; samples were also obtained on Days 15, 18, 21, 24, 28, 32, 36, 40, 50, and 64. Values shown are for $AUC_{0\text{-}t}$. Due to the low number of animals on test, individual animal data is shown.

ADA = anti-drug antibodies; ECG = electrocardiogram; F = female; FIA = Freund's Incomplete Adjuvant; HuMab-CD38 = anti-cynomolgus CD38 mAb; h = hour; ID = identification; IgG = immunoglobulin G; IgM = immunoglobulin M; IHC = immunohistochemistry; IV = intravenous; KLH = Keyhole Limpet Hemocyanin; M = male; mAb = monoclonal antibody; min. = minute; No. = number; NOAEL = No Observed Adverse Effect Level; SC = subcutaneous; TDAR = T-cell dependent antibody response; TK = toxicokinetics

(Continued)

Test Article: HuMab-CD38 [a]

Report Title: HuMab-CD38 ([redacted]): Pilot Toxicology and Pharmacokinetic Study in Cynomolgus Monkeys with a Two Month Recovery Period

DOSING AND RECOVERY PERIOD

Dose (mg/kg/week)	**0 (Control)**				**20**				**100**			
No. of Animals	M:2		F:2		M:2		F:2		M:2		F:2	
Animal ID No.	1M [b]	2M [c]	7F [b]	8F [c]	3M [b]	4M [c]	9F [b]	10F [c]	5M [b]	6M [c]	11F [b]	12F [c]
Noteworthy Findings												
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0	0	0	0	0
Body Weight	-	-	-	-	-	-	-	-	-	-	-	-
Clinical Observations	-	-	-	-	-	-	-	-	-	-	-	-
Physical Examination	-	-	-	-	-	-	-	-	-	-	-	-
Body Temperature	-	-	-	-	-	-	-	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-	-	-	-	-	-	-	-
Electrocardiography	-	-	-	-	-	-	-	-	-	-	-	-
Heart Rate	-	-	-	-	-	-	-	-	-	-	-	-
Hematology [d]												
Hemoglobin (g/dL)												
Pre-dose	11.8 [e]	14.7	12.6	13.8	13.5	13.2	14.5	13.7	13.7	13.4	11.2 [e]	14.8
Day 2	11.4	11.4	11.5	12.3	ND [f]	13.0	12.1	12.5	12.5	12.8	10.6	11.6
Day 8	11.7	12.8	12.8	ND [f]	10.0	ND [f]	6.8	10.5	10.1	8.3	10.0	10.1
Day 11 (necropsy main study group)	11.5		11.6		9.1		7.4		9.3		10.0	
Day 15		11.1		11.9		9.9		9.2		6.0		10.2
Day 21		11.7		12.7		9.4		10.3		6.0		9.8
Day 28		12.7		13.0		11.5		12.3		7.6 [g]		10.4
Day 36		11.9		12.6		12.7		13.4		9.1		12.5
RBC (10^{12}/L)												
Pre-dose	6.59 [e]	7.59	6.96	6.78	7.06	6.70	6.81	6.47	7.56	6.94	6.01 [e]	7.64
Day 2	6.43	5.96	6.29	6.08	ND [f]	6.59	5.74	5.95	6.89	6.53	5.60	6.10
Day 8	6.48	6.58	6.83	ND [f]	5.36	ND [f]	2.99	5.09	5.56	4.45	5.31	5.26
Day 11 (necropsy main study group)	6.52		6.20		4.88		2.96		5.11		5.24	
Day 15		5.80		5.96		4.78		4.45		2.98		5.07
Day 21		6.12		6.19		4.17		4.72		2.73		4.66
Day 28		6.39		6.21		5.11		5.77		3.32 [g]		4.82
Day 36		6.01		6.00		5.59		6.16		4.28		5.61

(Continued)

Test Article: HuMab-CD38 [a]

Report Title: HuMab-CD38 ([redacted]): Pilot Toxicology and Pharmacokinetic Study in Cynomolgus Monkeys with a Two Month Recovery Period

[a] The study was conducted with HuMab-CD38, a human IgG1 mAb that specifically binds to human and cynomolgus monkey CD38.
[b] Animals assigned to the main study group; animals were euthanized on Day 11.
[c] Animals assigned to the recovery study group; animals were euthanized on Day 64.
[d] Only individual values were provided in the report; the data is shown for key time points only.
[e] Pre-dose repeat values (1M was repeated due to high white blood cell count; 11F was repeated due to clotting of the coagulation sample and low platelet count).
[f] ND due to clotting of sample.
[g] Pre-dose repeat value (6M was repeated due to low platelet count).

F = female; HuMab-CD38 = anti-cynomolgus CD38 mAb; ID = identification; IgG = immunoglobulin G; M = male; mAb = monoclonal antibody; ND = not determined; No. = number; RBC = red blood cell; - = No noteworthy findings

(Continued)

Test Article: HuMab-CD38 [a]

Report Title: HuMab-CD38 ([redacted]): Pilot Toxicology and Pharmacokinetic Study in Cynomolgus Monkeys with a Two Month Recovery Period

DOSING AND RECOVERY PERIOD

Dose (mg/kg/week)	**0 (Control)**				**20**				**100**			
No. of Animals	M:2		F:2		M:2		F:2		M:2		F:2	
Animal ID No.	1M [b]	2M [c]	7F [b]	8F [c]	3M [b]	4M [c]	9F [b]	10F [c]	5M [b]	6M [c]	11F [b]	12F [c]
Hematology (continued) [d]												
LUC (10^9/L)												
Pre-dose	0.07 [e]	0.14	0.09	0.11	0.09	0.14	0.08	0.09	0.07	0.08	0.07 [e]	0.11
Day 2	0.06	0.15	0.14	0.20	ND [f]	0.02	0.01	0.01	0.04	0.00	0.05	0.07
Day 8	0.02	0.13	0.07	ND [f]	0.08	ND [f]	0.07	0.06	0.14	0.03	0.05	0.29
Day 11 (necropsy main study group)	0.04		0.11		0.05		0.06		0.09		0.05	
Day 15		0.10		0.11		0.08		0.09		0.04		0.13
Day 21		0.18		0.12		0.08		0.05		0.03		0.19
Day 28		0.21		0.07		0.08		0.02		0.06 [g]		0.28
Day 36		0.09		0.05		0.03		0.07		0.05		0.15
Hct (L/L)												
Pre-dose	0.399 [e]	0.474	0.458	0.497	0.478	0.455	0.440	0.444	0.468	0.476	0.389 [e]	0.539
Day 2	0.408	0.382	0.424	0.423	ND [f]	0.437	0.362	0.413	0.420	0.432	0.365	0.412
Day 8	0.410	0.426	0.464	ND [f]	0.360	ND [f]	0.221	0.356	0.349	0.277	0.350	0.367
Day 11 (necropsy main study group)	0.399		0.417		0.321		0.238		0.318		0.340	
Day 15		0.378		0.425		0.354		0.313		0.223		0.367
Day 21		0.408		0.445		0.329		0.354		0.214		0.347
Day 28		0.431		0.441		0.389		0.411		0.265 [g]		0.385
Day 36		0.401		0.433		0.422		0.470		0.316		0.461
Ret (%)												
Pre-dose	0.3 [e]	0.2	0.3	0.2	0.3	0.4	0.1	0.3	0.1	0.5	0.6 [e]	0.3
Day 2	1.0	1.3	1.7	0.5	ND [f]	0.3	0.4	0.8	0.3	1.0	1.3	0.9
Day 8	2.3	1.9	2.2	ND [f]	1.1	ND [f]	20.3	5.6	1.6	1.2	3.6	5.9
Day 11 (necropsy main study group)	1.9		2.4		5.4		16.9		3.7		3.2	
Day 15		3.1		1.8		8.2		6.4		11.4		6.9
Day 21		4.4		1.8		11.1		10.0		7.3		6.1
Day 28		3.1		1.2		3.1		1.5		6.9 [g]		7.4
Day 36		2.4		1.1		0.8		0.9		6.0		2.2

(Continued)

2.6.7.6　反復投与毒性試験：重要な試験以外の試験（続き）

Test Article: HuMab-CD38 [a]

Report Title: HuMab-CD38 ([redacted]): Pilot Toxicology and Pharmacokinetic Study in Cynomolgus Monkeys with a Two Month Recovery Period

[a] The study was conducted with HuMab-CD38, a human IgG1 mAb that specifically binds to human and cynomolgus monkey CD38.
[b] Animals assigned to the main study group; animals were euthanized on Day 11.
[c] Animals assigned to the recovery study group; animals were euthanized on Day 64.
[d] Only individual values were provided in the report; the data is shown for key time points only.
[e] Pre-dose repeat values (1M was repeated due to high white blood cell count; 11F was repeated due to clotting of the coagulation sample and low platelet count).
[f] ND due to clotting of sample.
[g] Pre-dose repeat value (6M was repeated due to low platelet count).

F = female; Hct = Haematocrit; HuMab-CD38 = anti-cynomolgus CD38 mAb; ID = identification; IgG = immunoglobulin G; LUC = Large unclassified cells; M = male; mAb = monoclonal antibody; ND = not determined; No. = number; Ret = Reticulocytes

(Continued)

Test Article: HuMab-CD38 [a]

Report Title: HuMab-CD38 ([redacted]): Pilot Toxicology and Pharmacokinetic Study in Cynomolgus Monkeys with a Two Month Recovery Period

DOSING AND RECOVERY PERIOD

Dose (mg/kg/week)	**0 (Control)**				**20**				**100**			
No. of Animals	M:2		F:2		M:2		F:2		M:2		F:2	
Animal ID No.	1M [b]	2M [c]	7F [b]	8F [c]	3M [b]	4M [c]	9F [b]	10F [c]	5M [b]	6M [c]	11F [b]	12F [c]
Hematology (continued) [d]												
WBC ($x10^9$/L)												
Pre-dose	12.77 [e]	9.67	8.37	15.51	9.64	13.28	7.29	15.65	13.01	14.00	11.17 [e]	9.45
Day 2	15.05	16.16	11.81	15.77	ND [f]	8.65	7.83	11.18	12.71	7.48	14.60	15.40
Day 8	11.58	12.97	10.31	ND [f]	6.57	ND [f]	5.48	6.48	7.51	8.52	5.95	7.19
Day 11 (necropsy main study group)	10.96		10.34		6.62		3.67		6.96		6.76	
Day 15		9.47		9.73		7.67		7.60		8.97		6.05
Day 21		12.78		10.19		7.02		8.21		3.79		5.87
Day 28		15.65		10.59		7.90		6.38		4.61 [g]		5.81
Day 36		9.79		12.45		10.54		11.43		4.02		6.51
Lymphocytes (10^9/L)												
Pre-dose	3.38 [e]	5.71	3.57	5.15	3.52	7.49	2.31	5.42	3.96	5.43	3.08 [e]	5.14
Day 2	5.37	5.86	6.17	5.61	ND [f]	1.27	1.14	1.51	1.55	0.54	1.01	2.37
Day 8	3.11	4.93	3.57	ND [f]	1.41	ND [f]	0.79	0.95	1.39	0.40	0.65	1.66
Day 11 (necropsy main study group)	3.94		4.91		1.05		0.45		0.94		0.53	
Day 15		4.71		3.74		1.21		1.45		0.33		0.95
Day 21		8.18		4.35		2.53		2.37		0.31		1.01
Day 28		10.16		4.28		3.04		1.84		0.64 [g]		2.69
Day 36		4.62		3.21		1.74		2.18		0.85		2.23

[a] The study was conducted with HuMab-CD38, a human IgG1 mAb that specifically binds to human and cynomolgus monkey CD38.
[b] Animals assigned to the main study group; animals were euthanized on Day 11.
[c] Animals assigned to the recovery study group; animals were euthanized on Day 64.
[d] Only individual values were provided in the report; the data is shown for key time points only.
[e] Pre-dose repeat values (1M was repeated due to high white blood cell count; 11F was repeated due to clotting of the coagulation sample and low platelet count).
[f] ND due to clotting of sample.
[g] Pre-dose repeat value (6M was repeated due to low platelet count).

F = female; HuMab-CD38 = anti-cynomolgus CD38 mAb; ID = identification; IgG = immunoglobulin G; M = male; mAb = monoclonal antibody; ND = not determined; No. = number; WBC = white blood cell

(Continued)

Test Article: HuMab-CD38 [a]

Report Title: HuMab-CD38 ([redacted]): Pilot Toxicology and Pharmacokinetic Study in Cynomolgus Monkeys with a Two Month Recovery Period

DOSING AND RECOVERY PERIOD

Dose (mg/kg/week)	**0 (Control)**				**20**				**100**			
No. of Animals	M:2		F:2		M:2		F:2		M:2		F:2	
Animal ID No.	1M [b]	2M [c]	7F [b]	8F [c]	3M [b]	4M [c]	9F [b]	10F [c]	5M [b]	6M [c]	11F [b]	12F [c]
Serum Chemistry [d]												
Total Bilirubin (µmol/L)												
Pre-dose	1.7	5.9	1.9	2.5	1.9	3.3	6.4	2.4	1.9	1.7	2.3	1.4
Day 2	1.5	2.7	1.7	2.7	2.8	14.6	16.0	5.0	6.4	5.0	8.9	4.0
Day 8	1.3	3.1	1.6	3.3	2.6	6.4	8.8	6.7	2.1	9.7	3.4	5.8
Day 11 (necropsy main study group)	2.5		1.4		4.0		12.3		2.9		5.5	
Day 15		3.9		2.0		5.2		19.9		3.2		4.8
IgA (mg/dL)												
Pre-dose	397	163	256	225	304	225	162	224	126	203	277	125
Day 15		190		211		175		124		59		137
Day 21		209		225		170		158		44		112
Day 28		198		243		168		169		38		98
Day 36		184		228		164		164		34		107
Day 50		186		294		155		150		87		132
Day 64 (necropsy recovery group)		182		264		159		125		115		133
IgG (mg/dL)												
Pre-dose	1433	903	1004	1125	947	913	994	921	975	753	803	982
Day 15		862		1070		763		900		448		705
Day 21		911		1118		760		1077		339		572
Day 28		1028		1191		847		1158		302		560
Day 36		1018		1075		835		1071		378		671
Day 50		1047		1212		825		1098		936		832
Day 64 (necropsy recovery group)		1052		1226		946		1001		966		926

[a] The study was conducted with HuMab-CD38, a human IgG1 mAb that specifically binds to human and cynomolgus monkey CD38.
[b] Animals assigned to the main study group; animals were euthanized on Day 11.
[c] Animals assigned to the recovery study group; animals were euthanized on Day 64.
[d] Only individual values were provided in the report; the data is shown for key time points only.

F = female; HuMab-CD38 = anti-cynomolgus CD38 mAb; ID = identification; IgA = immunoglobulin A; IgG = immunoglobulin G; M = male; mAb = monoclonal antibody; No. = number

(Continued)

Test Article: HuMab-CD38 [a]

Report Title: HuMab-CD38 ([redacted]): Pilot Toxicology and Pharmacokinetic Study in Cynomolgus Monkeys with a Two Month Recovery Period

DOSING AND RECOVERY PERIOD

Dose (mg/kg/week)	**0 (Control)**				**20**				**100**			
No. of Animals	M:2		F:2		M:2		F:2		M:2		F:2	
Animal ID No.	1M [b]	2M [c]	7F [b]	8F [c]	3M [b]	4M [c]	9F [b]	10F [c]	5M [b]	6M [c]	11F [b]	12F [c]
Serum Chemistry (continued) [d]												
IgM (mg/dL)												
Pre-dose	202	133	110	191	106	130	99	134	98	102	215	82
Day 15		160		223		91		65		40		74
Day 21		170		228		89		79		31		57
Day 28		153		220		89		78		29		51
Day 36		130		201		78		89		27		54
Day 50		138		235		74		76		44		60
Day 64 (necropsy recovery group)		215		252		135		64		103		63
Urinalysis	-	-	-	-	-	-	-	-	-	-	-	-
Gross Pathology												
Thymus, small [e]	-	-	-	-	-	-	-	-	P	-	P	-
Organ weights (absolute) [f]												
Thymus (g)	1.70	-	3.13	-	-	-	-	-	0.54x	-	0.18x	-
Histological findings												
Thymus, atrophy	-	-	-	-	+++P	-	++P	-	++++P	-	++++P	+P
Peyer's patches, lymphoid atrophy	-	-	-	-	++P	-	-	-	+++P	-	-	-
Spleen, lymphoid atrophy	-	-	-	-	-	-	+P	-	++P	-	++P	-
Mandibular lymph node, lymphoid depletion	-	-	-	-	-	-	-	-	++P	-	-	-
Mesenteric lymph node, lymphoid depletion	-	-	-	-	-	-	-	-	++P	+P	-	-
Spinal cord, multifocal inflammation	-	-	-	-	-	-	-	-	-	-	++P	-
Spinal cord, focal inflammatory cell infiltration	-	-	-	-	-	+P	-	-	-	+P [g]	-	-

[a] The study was conducted with HuMab-CD38, a human IgG1 mAb that specifically binds to human and cynomolgus monkey CD38.
[b] Animals assigned to the main study group; animals were euthanized on Day 11.
[c] Animals assigned to the recovery study group; animals were euthanized on Day 64.
[d] Only individual values were provided in the report; the data is shown for key time points only.
[e] The findings seen in the two high-dose (100 mg/kg) animals at the Day 11 necropsy (small size and decreased weight of thymus) had resolved and were not present in recovery group animals necropsied on Day 64.
[f] For controls, the absolute weights are shown. For treated groups, multiples of control are shown.
[g] Finding in both spinal cord and sciatic nerve.

F = female; HuMab-CD38 = anti-cynomolgus CD38 mAb; ID = identification; IgG = immunoglobulin G; IgM = immunoglobulin M; M = male; mAb = monoclonal antibody; No. = number; P = finding present; - = No noteworthy findings; + = minimal; ++ = mild; +++ = moderate; ++++ = marked

(Continued)

Test Article: HuMab-CD38 [a]

Report Title: HuMab-CD38 ([redacted]): Pilot Toxicology and Pharmacokinetic Study in Cynomolgus Monkeys with a Two Month Recovery Period

DOSING AND RECOVERY PERIOD

Dose (mg/kg/week)	**0 (Control)**				**20**				**100**			
No. of Animals	M:2		F:2		M:2		F:2		M:2		F:2	
Animal ID No.	1M [b]	2M [c]	7F [b]	8F [c]	3M [b]	4M [c]	9F [b]	10F [c]	5M [b]	6M [c]	11F [b]	12F [c]
Direct Coombs Test – IgG positive results [d]												
Day 8	-	-	-	-	positive	positive	positive	positive	positive	positive	positive	positive
Day 28		-		-		positive		-		positive		positive
Day 64		-		-		-		-		-		positive
TDAR to KLH [e]												
IgG titre (1:×)												
Day 1	800	400	400	1600	400	400	800	1600	1600	400	800	800
Day 8	12800	12800	12800	25600	800	25600	3200	6400	6400	800	3200	6400
Day 11	1600	1600	3200	3200	400	1600	400	1600	6400	800	1600	6400
Day 15		6400		6400		3200		1600		400		800
Day 22		12800		1600		3200		1600		400		800
Day 29		3200		25600		3200		400		800		1600
Day 36		3200		25600		3200		<100		800		1600
Day 43		400		12800		3200		100		800		1600
Day 50		800		3200		3200		<100		51200		3200
Day 55		3200		1600		1600		6400		800		1600
IgM titre (1:×)												
Day 1	800	800	800	800	400	1600	800	800	800	400	400	3200
Day 8	3200	3200	1600	12800	800	400	1600	200	800	1600	800	800
Day 11	3200	3200	800	6400	400	1600	400	400	800	800	3200	1600
Day 15		800		6400		1600		200		<100		400
Day 22		100		6400		400		100		100		100
Day 29		200		1600		200		<100		<100		100
Day 36		200		800		200		<100		<100		100
Day 43		<100		1600		200		100		<100		<100
Day 50		3200		800		200		<100		100		<100
Day 55		800		1600		200		<100		<100		100
Bone marrow evaluation (Days 11 and 64) [f]												
Increased normoblasts	-	-	-	-	P	-	P	-	-	-	P	NA
Increased mitotic promyelocytes	-	-	-	-	-	-	P	-	-	-	-	NA
Lymphopenia	-	-	-	-	P	-	P	-	P	-	P	NA

(Continued)

2.6.7.6　反復投与毒性試験：重要な試験以外の試験（続き）

Test Article: HuMab-CD38 [a]

Report Title: HuMab-CD38 ([redacted]): Pilot Toxicology and Pharmacokinetic Study in Cynomolgus Monkeys with a Two Month Recovery Period

[a] The study was conducted with HuMab-CD38, a human IgG1 mAb that specifically binds to human and cynomolgus monkey CD38.
[b] Animals assigned to the main study group; animals were euthanized on Day 11.
[c] Animals assigned to the recovery study group; animals were euthanized on Day 64.
[d] Animals are noted as having a positive Coombs test or not; only the days on which a positive test result was seen are noted here.
[e] Only individual values were provided in the report; the data is shown for key time points only.
[f] Bone marrow smears were obtained from main study animals at necropsy Day 11 and from recovery animals at necropsy on Day 64. Samples from No. 12F were unsuitable for assessment (NA).

ADA = anti-drug antibodies ; F = female; HuMab-CD38 = anti-cynomolgus CD38 mAb; ID = identification; IgG = immunoglobulin G; IgM = immunoglobulin M; KLH = Keyhole Limpet Hemocyanin; M = male; mAb = monoclonal antibody; NA = not applicable; No. = number; P = finding present; TDAR = T-cell dependent antibody response; - = No noteworthy findings

(Continued)

2.6.7.6 反復投与毒性試験：重要な試験以外の試験（続き）

Test Article: HuMab-CD38 [a]

Report Title: HuMab-CD38 ([redacted]): Pilot Toxicology and Pharmacokinetic Study in Cynomolgus Monkeys with a Two Month Recovery Period

DOSING AND RECOVERY PERIOD

Dose (mg/kg/week)	**0 (Control)**				**20**				**100**			
No. of Animals	M:2		F:2		M:2		F:2		M:2		F:2	
Animal ID No.	1M [b]	2M [c]	7F [b]	8F [c]	3M [b]	4M [c]	9F [b]	10F [c]	5M [b]	6M [c]	11F [b]	12F [c]

Additional Examinations

Immunohistochemistry

HuMab-CD38 binds to target sites of the lymphoid tissues both *in vivo* and *in vitro*. *In vivo*, binding of HuMab-CD38 persisted in tissues of treated animals until death. *In vitro*, immunostaining was dependent on pre-treatment of sections with HuMab-CD38. Following pre-treatment with HuMab-CD38, there was widespread staining of tissues, including extrafollicular lymphoid tissue, thymus, renal glomeruli, and bone marrow, in all 20 and 100 mg/kg-dosed animals, suggesting the presence of CD38 expressing lymphocytes or other tissue components in these organs.
For details, refer to Mod4.2.3.2.1/509809/Sec4.4.4 and Mod4.2.3.2.1/Sec6/Tab1 and Tab2.

Flow Cytometry

There was a marked depletion in $CD4^+$ and $CD8^+$ T cells expressing CD38 in animals receiving 20 or 100 mg/kg; this finding was observed on Day 8 in animals from both dose groups, although there were some indications that the depletion may have begun as early as Day 1 in animals administered 100 mg/kg. Both $CD4^+$ and $CD8^+$ T cells increased during the recovery period. The overall T cell population number reflected these marked diminutions in cell levels, although there appeared to be a refractory rebound in cell number for animals receiving 100 mg/kg. Depletion was also seen in the effector NK phenotype expressing CD38 ($CD16^+CD38^+CD8^+$). This was mimicked in the $CD16^+CD8^+$ NK population suggesting that many, if not all, effector NK cells express CD38. Mature B cells not expressing CD27 ($CD27^-CD21^+CD40^+CD20^+$) showed a marked reduction in cell numbers. This depletion appeared to occur faster in animals receiving 100 mg/kg compared to animals receiving 20 mg/kg (initiating Day 1 vs. Day 8, respectively), and the $CD27^-CD21^+CD40^+CD20^+$ cells did not recover by the last sampling point at Day 64. Memory B cells expressing CD38 ($CD27^+CD38^+CD20^+$) also showed a marked depletion in treated groups, as did B cells expressing CD38 and B cells expressing CD27; as noted previously, recovery in these cell populations was not complete by Day 64. Monocytes generally appeared not to be affected by dosing; the slight reduction in cell numbers was transient in nature and thus not deemed to be dose-related.
Within the lymph nodes, $CD4^+$ T cells expressing CD38 did not show the same degree of depletion as with the peripheral cells. The $CD8^+$ T cells expressing CD38 showed a more notable depletion. Overall, these patterns were mimicked in the main $CD4^+$ and $CD8^+$ T cell populations for both treated groups. NK cells within the lymph node constituted <1% of the cells and therefore any effect on this cell population could not be assessed. Mature B cells not expressing $CD27^-$ ($CD27^-CD21^+CD40^+CD20^+$) within the lymph node showed very little change in percentage. This was also true for all of the other B cell populations assessed in the lymph node samples. The $CD14^+$ monocytes (and subsets) accounted for less than 2% of the population of cells and could therefore not be evaluated further.
Data obtained from flow cytometry analysis of terminally obtained bone marrow samples were not interpretable.
For details, refer to Mod4.2.3.2.1/509809/App18 and Mod4.2.3.2.1/509809/App18/Tab1 through Tab49.

[a] The study was conducted with HuMab-CD38, a human IgG1 mAb that specifically binds to human and cynomolgus monkey CD38.
[b] Animals assigned to the main study group; animals were euthanized on Day 11.
[c] Animals assigned to the recovery study group; animals were euthanized on Day 64.

F = female; HuMab-CD38 = anti-cynomolgus CD38 mAb; IgG = immunoglobulin G; M = male; mAb = monoclonal antibody; NK = natural killer; No. = number

2.6.7.7 反復投与毒性試験

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article**: Daratumumab

Species/Strain: Chimpanzee
Duration of Dosing: 6 weeks (once weekly)
Study No.: 8754-0701
Age at First Dose: 10 - 15 years old
Duration of Postdose Recovery: 91 or 105 days [a]
Location in CTD: 4.2.3.2.2
Date of First Dose: [redacted], [redacted]
Route: IV (30 min.[vehicle]; 30 min.-1 h [daratumumab]) [b,c]
GLP Compliance: Yes

Vehicle/Formulation: Vehicle: 25 mmol/L sodium acetate, 60 mmol/L sodium chloride, 140 mmol/L mannitol, 0.006% polysorbate 20 pH 5.5 / Daratumumab (HuMax-CD38): 21.1 mg/mL in sterile pyrogen free 0.9% NaCl (125 mL dilution)

Special Features: ECG, BP, pulse rate, RR, and body temperature (pre-dose, on days of dosing[30 mins. and 24 h postdose] and during recovery); ophthalmic examinations (pre-study, 24 h after Dose 6, and once during recovery); direct anti-globulin effects[pre-study, 24 h postdose vehicle or test article administration, pre-Dose 1 (Group 2 only) and during recovery]; Flow cytometry for immunophenotyping of peripheral blood subsets (pre-study, prior to vehicle or test article administration, 24 h after Dose 1, and during recovery); Biopsies of skin and inguinal lymph node, and bone marrow aspirates were taken for flow cytometry and IHC analysis (pre-study, 48 h after Dose 3, 24 h after Dose 6, and during recovery); Serum TK and ADA were measured. Serum cytokine levels (TNF-α, IL-6, and IFN-γ) were measured in animal No. 92A016. (Animals were sedated for all procedures.)

No Observed Adverse Effect Level: NA [d]

DOSING AND RECOVERY PERIOD				
Dose (mg/kg/week)	0→5 [b]		0→25 [c]	
No. of Animals	M:1	F:2 [e]	M:1	F:1
Toxicokinetics: [f,g]				
No. of Animals	M:1	F: 1	M:1	F:1
Animal ID No.	96A009	95A015	96A015	96A017
AUC_{0-t} (μg·h/mL) [h]				
Study Day 7 / (Dosing Day 0)	2,185	2,799		
Study Day 21 / (Dosing Day 14)	11,309			
Study Day 22 / (Dosing Day 0)			25,885	39,158
Study Day 35 / (Dosing Day 14)			39,995	62,112
Study Day 42 / (Dosing Day 35)	21,450			
Study Day 56 / (Dosing Day 35)			146,729	201,462
C_{max} (μg/mL)				
Study Day 7 / (Dosing Day 0)	100	86		
Study Day 21 / (Dosing Day 14)	129			
Study Day 22 / (Dosing Day 0)			612	778
Study Day 35 / (Dosing Day 14)			630	599
Study Day 42 / (Dosing Day 35)	129			
Study Day 56 / (Dosing Day 35)			695	967

(Continued)

2.6.7.7　反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period　**Test Article**: Daratumumab

[a] The treatment period was followed by a recovery period of 105 or 91 days for low (5 mg/kg) and high (25 mg/kg) dose animals, respectively.
[b] Animals assigned to Group 1 were administered the vehicle on Day 0, followed by a 5 mg/kg IV infusion (30 min.) of daratumumab on Day 7; dosing occurred weekly for 6 weeks until Day 42.
[c] Animals assigned to Group 2 were administered the vehicle on Day 7. In order to prevent exaggerated cytokine release, animals received a 10 mg pre-dose of daratumumab via IV injection on Day 21, followed by a 25 mg/kg IV infusion (1 h) of daratumumab administered 24 h later on Day 22; infusion (30 min.) occurred weekly for 6 weeks until Day 56.
[d] A NOAEL was not reached during the study.
[e] On Study Day 15, female No. 95A015 had a non-drug-related accident and treatment was discontinued. She was replaced by another female chimpanzee; that replacement animal (No. 92A016), however, died 1.5 h after the Study Day 7 infusion. As only limited TK samples (pre-dose, post-dose, and terminal [ie, 1.5 h post-dose]) were obtained for No. 92A016, data for that animal are not provided here.
[f] The actual day of dosing is shown, followed by the standardized dosing day in parentheses. Days correspond to the first, third, and sixth administrations. Blood samples were collected for serum prior to infusion and 0.58, 2, 3.5, 6.5, 24, 48, and 144 or 168 h after the initiation of the first, third, and sixth doses. Additional blood samples were collected after the sixth infusion in Group 1 (96, 240, 360, 528, 2016, 2184, 2352, and 2520 h) and Group 2 (96, 240, 360, 528, 1680, 1848, 2016, and 2184 h).
[g] Only exposure data is provided here; refer to Mod2.6.4, the Nonclinical Pharmacokinetics Written Summary and to Nonclinical Pharmacokinetics Tabulated Summary 2.6.5.4A for additional TK parameters.
[h] In the 5 mg/kg cohort, the last quantifiable TK sample was collected 168 h after the first and third dose, and 528 h after the sixth dose. In the 25 mg/kg cohort, the last quantifiable TK sample was collected 144 h after the first dose, 168 h after the third dose, and 528 h after the sixth dose.

ADA = anti-drug antibodies; AUC = area under the serum concentration versus time curve from time 0 to defined time t; BP = blood pressure; C_{max} = maximum serum concentration; ECG = electrocardiogram; F = female; GLP = Good Laboratory Practice; h = hour; IFN-γ = interferon-gamma; IHC = immunohistochemistry; IL-6 = interleukin-6; IV = intravenous; M = male; min. = minute; NA = not applicable; No. = number; NOAEL = No Observed Adverse Effect Level; RR = respiration rate; TK = toxicokinetics; TNF-α = Tumor Necrosis Factor-α

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article**: Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1	F:2		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Died or Sacrificed Moribund	0	0	1	0	0
ADA	-	-	-	-	-
Body Weight	-	-	-	-	-
Food Consumption	-	-	-	-	-
Clinical Observations					
Increased mucous production (sinus and/or trachea) [b]	P (~5 min. [17 mL] into Dose 1)	P (~5 min. [17 mL] into Dose 1)	P (~10 min. [34 mL] into Dose 1)	P (~12 min. [20 mL] into Dose 1; still observed in trachea ~30 min [50 mL] into Dose 1)	P (Post-10 mg loading dose, day prior to Dose 1, and ~15 min. [25 mL] into Dose 1)
Evacuation of bowel [b]	P (~10 min. [33 mL] into Dose 1, and 30 min. post-Dose 1)	-	P (30 min. post-Dose 1)	P (37 min. post-Dose 1)	-
Diarrhea [c,d]	-	-	-	P (32/326) (Days 52, 75, 76, 79, 86-93, 95-106, 116 [majority of instances seen ~Days 86-106, 30-50 days post-Dose 6])	P (8/326) (Days 103-105 [ie, 47-49 days post-Dose 6], 114, 115, 127)
Blood in stool [c]	-	-	-	P (1/326) (Day 105 [ie, 49 days post-Dose 6])	-
Soft stool [c]	P (33/340) (Days 0-6, 9, 10, 12, 13, 20, 23, 29, 78, 105, 106, 140, 151-155, 157-159)	P (8/206) (Days 0, 1, 4, 5, 9, 99)	P (1/15) Day 30	P (128/326) (Days 12, 13, 53, 60, 67, 72, 77-90, 93-95, 97, 100, 101, 103-112, 114-116, 118-123, 126-138, 142-146, 150, 151, 153-161, 163-169)	P (23/326) (Days 10, 11, 38, 78, 95, 97, 102, 106, 113-115, 120, 121, 126, 150-152, 158, 167, 168)

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Clinical observations noted during dosing are described in the clinical observations text (refer to the Results section of the report, Mod 4.2.3.2.2/8754-0701/Sec 7.1) and are not included in the report tables.

[c] For all other observations the number of instances a finding was seen in each animal over the total possible instances is given. Observations were recorded twice a day, and are reported from the day of vehicle administration to study termination (Days 0–169 for the group 1 animal No. 96A009 [340 instances], Days 0-102 for animal No. 95A015 [206 instances], and Days 28-35 for replacement female No. 92A016, which died 1.5 h after dosing [15 instances]; Days 7-169 for the group 2 animals [326 instances]); data is followed by the period of time when findings were seen.

[d] Animal No. 96A015 and No. 96A017 received veterinary treatment with antimicrobials and supportive care during the episodes of diarrhea/soft feces, but were slow to respond to treatment. Diagnostic exams did not indicate a specific cause for the diarrhea; therefore, daratumumab administration cannot be ruled out as a possible contributing factor.

ADA = anti-drug antibodies; F = female; h = hour; ID = identification; IV = intravenous; M = male; min. = minute; No. = number; P = finding present; - = No noteworthy findings

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article**: Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1		F:2	M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Clinical Observations (Continued)					
Sneezing [b]	-	-	P (~10 min. [34 mL] into Dose 1)	P (~12 min. [20 mL] into Dose 1; finding subsided ~30 min [50 mL] into Dose 1)	P (~15 min. [25 mL] into Dose 1)
Reduced appetite/not eating [c]	P (3/340) (Days 105, 126, 127)	-	-	P (5/326) (Days 24, 26, 110, 159)	P (14/326) (Days 40, 61, 62, 103, 104, 110, 111, 117, 124, 138, 159, 168)
Pallor, mucous membrane [b]	-	-	P (16 min. [55 mL] into Dose 1)	-	P (~26 min. [44 mL] into Dose 1)
Hypoactivity/depression [c]	-	-	-	P (6/326) (Days 22, 23, 26, 37, 49, 112)	P (2/326) (Days 22, 23)
Labored breathing [b]	-	-	P (16 min. [55 mL] into Dose 1)	-	-
Obtunded [b]	-	-	-	-	P (Post-10 mg loading dose, day prior to Dose 1)
Production of foaming fluid (trachea and nares) [b]	-	-	P (~1.5 h post-Dose 1)	-	-
Respiratory arrest [b]	-	-	P (~1.5 h post-Dose 1)	-	-
ECGs	-	-	-	-	-
Blood pressure	-	-	-	-	-
Pulse rate	-	-	-	-	-
Respiratory rate	-	-	-	-	-
Body temperature	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Clinical observations noted during dosing are described in the clinical observations text (refer to the Results section of the report, (refer to the Results section of the report, Mod4.2.3.2.2/8754-0701/Sec 7.1).

[c] For all other observations, the number of instances a finding was seen in each animal over the total possible instances is given. Observations were recorded twice a day, and are reported from the day of vehicle administration to study termination (Days 0-169 for the group 1 animal No. 96A009 [340 instances], Days 0-102 for animal No. 95A015 [206 instances], and Days 28-35 for replacement female No. 92A016, which died 1.5 h after dosing [15 instances]; Days 7-169 for the group 2 animals [326 instances]); data is followed by the period of time when findings were seen.

ECGs = electrocardiograms; F = female; h = hour; ID = identification; IV = intravenous; M = male; min. = minute; No. = number; P = finding present; - = No noteworthy findings

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1	F:2		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Hematology [b]					
Platelets (x10^3/mm^3)					
Pre-dose	244	**144**	249	237	226
PD 1 [c]	210	184	NA	**61**	**129**
PD 2 [c]	183	**66**	NA	**34**	**96**
PD 5 [c]	**53**	285	NA	**17**	**38**
Day 71/85 [d]	**137**	**177**	NA	**13**	**28**
Day 98	228	NA	NA	NA	NA
Day 112	NA	NA	NA	**5**	**10**
Day 133	282	NA	NA	**52**	**43**
Day 147	231	NA	NA	**170**	**147**
Neutrophils (%)					
Pre-dose	65.7	**79.6**	63.0	48.8	67.0
PD 1 [c]	**78.5**	**93.0**	NA	77.5	**86.8**
PD 2 [c]	72.0	**86.4**	NA	**79.9**	**83.4**
PD 3 [c]	**80.7**	NA	NA	**84.6**	**85.7**
PD 4 [c]	70.2	NA	NA	**83.0**	**86.2**
PD 5 [c]	59.7	59.8	NA	**78.0**	**79.6**
PD 6 [c]	66.0	NA	NA	**81.5**	**79.9**
Day 71/85 [d]	60.0	60.0	NA	70.9	55.2
Day 147	52.8	NA	NA	71.1	44.9

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Only individual values were provided in the report; the data is shown for key time points only. Values in bold are outside of the normal range of typical hematology values shown in Mod4.2.3.2.2/8754-0701/TabF.

[c] Time points noted as PD are for 24 h post-dose samples.

[d] Day 71 for the group 1 animals; Day 85 for the group 2 animals, ie, 29 days after Dose 6.

F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; No. = number; PD = post-dose

(Continued)

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1	F:2		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Hematology (Continued) [b]					
Lymphocytes (%)					
Pre-dose	27.6	**17.6**	27.2	42.1	24.0
PD 1 [c]	**16.8**	**6.3**	NA	**19.4**	**10.6**
PD 2 [c]	22.3	**10.6**	NA	**16.2**	**12.6**
PD 3 [c]	**17.8**	NA	NA	**12.4**	**11.3**
PD 4 [c]	23.6	NA	NA	**13.3**	**11.0**
PD 5 [c]	34.5	31.6	NA	20.4	**16.2**
PD 6 [c]	26.8	NA	NA	**14.4**	**15.9**
Day 71/85 [d]	33.4	35.5	NA	23.8	37.4
Day 147	39.4	NA	NA	24.3	46.5
Red cell count ($\times 10^6/mm^3$)					
Pre-dose	5.29	**4.59**	**3.73**	5.47	5.06
PD Vehicle[c]	5.13	4.67	**4.01**	5.37	4.79
PD 1 [c]	5.04	**4.56**	NA	5.29	5.30
PD 2 [c]	4.92	**4.15**	NA	4.70	4.69
PD 3 [c]	4.85	NA	NA	4.81	**4.31**
PD 4 [c]	**4.57**	NA	NA	**3.82**	**3.88**
PD 5 [c]	**4.58**	**3.63**	NA	**3.41**	**3.72**
PD 6 [c]	**4.30**	NA	NA	**3.44**	**3.81**
Day 71/85 [d]	**3.80**	**4.19**	NA	**3.32**	**4.41**
Day 98	**4.17**	NA	NA	NA	NA
Day 112	NA	NA	NA	**2.67**	**4.55**
Day 126	4.7	NA	NA	**3.08**	**3.95**
Day 133	5.04	NA	NA	**3.75**	**3.90**
Day 140	5.08	NA	NA	**3.84**	**4.03**
Day 147	4.91	NA	NA	**3.66**	**3.89**

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Only individual values were provided in the report; the data is shown for key time points only. Values in bold are outside of the normal range of typical hematology values shown in Mod4.2.3.2.2/8754-0701/TabF.

[c] Time points noted as PD are for 24 h post-dose samples.

[d] Day 71 for the group 1 animals; Day 85 for the group 2 animals, ie, 29 days after Dose 6.

F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; No. = number; PD = post-dose

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5			0→25
No. of Animals	M:1	F:2		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Hematology (Continued) [b]					
Hemoglobin (g/dL)					
Pre-dose	15.1	13.6	**11.0**	**16.0**	13.4
PD Vehicle [c]	14.6	13.8	**11.8**	15.5	**12.5**
PD 1 [c]	14.5	13.6	NA	14.9	13.3
PD 2 [c]	14.4	**12.4**	NA	13.5	**12.2**
PD 3 [c]	13.8	NA	NA	**12.2**	**11.1**
PD 4 [c]	13.1	NA	NA	**11.1**	**10.0**
PD 5 [c]	13.0	**11.2**	NA	**9.8**	**9.8**
PD 6 [c]	**12.3**	NA	NA	**10.1**	**10.0**
Day 71/85 [d]	**11.5**	13.0	NA	**9.8**	**12.2**
Day 98	12.8	NA	NA	NA	NA
Day 112	NA	NA	NA	**8.0**	**12.7**
Day 126	13.9	NA	NA	**9.8**	**11.1**
Day 133	14.9	NA	NA	**11.8**	**11.1**
Day 140	15.0	NA	NA	**12.1**	**11.7**
Day 147	14.5	NA	NA	**11.6**	**11.3**

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Only individual values were provided in the report; the data is shown for key time points only. Values in bold are outside of the normal range of typical hematology values shown in Mod4.2.3.2.2/8754-0701/TabF.

[c] Time points noted as PD are for 24 h post-dose samples.

[d] Day 71 for the group 1 animals; Day 85 for the group 2 animals, ie, 29 days after Dose 6.

F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; No. = number; PD = post-dose

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5			0→25
No. of Animals	M:1	F:2		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Coagulation [b]					
APTT (sec)					
Pre-dose	23.3	21.1	20.8	20.5	22.6
PD 1 [c]	31.5	24.9	NA	20.5	21.9
PD 2 [c]	23.3	21.1	NA	22.8	24.8
PD 3 [c]	22.2	NA	NA	25.8	34.3
PD 4 [c]	26.8	NA	NA	30.4	36.6
PD 5 [c]	27.0	22.5	NA	25.9	30.3
PD 6 [c]	29.3	NA	NA	31.3	33.8
Day 71/85 [d]	22.6	22.0	NA	27.4	22.9
Day 98	23.5	NA	NA	NA	NA
Day 112	NA	NA	NA	25.8	26.4
Day 126	24.8	NA	NA	27.6	29.4
Day 133	24.4	NA	NA	25.8	29.7
Day 140	23.4	NA	NA	23.4	25.9
Day 147	22.5	NA	NA	24.9	27.8

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.
[b] Only individual values were provided in the report; the data is shown for key time points only.
[c] Time points noted as PD are for 24 h post-dose samples.
[d] Day 71 for the group 1 animals; Day 85 for the group 2 animals, ie, 29 days after Dose 6.

APTT = activated partial thromboplastin time; F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; No. = number; PD = post-dose

(Continued)

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1	F:2		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Serum Chemistry [b]					
Potassium (mmol/L)					
Pre-dose	4.0	3.3	3.6	2.9	3.4
PD 1 [c]	3.8	**2.5**	NA	**2.4**	3.3
PD 2 [c]	**4.4**	**2.4**	NA	**2.1**	3.5
PD 3 [c]	3.7	NA	NA	**2.1**	3.2
PD 4 [c]	3.7	NA	NA	**2.1**	3.4
PD 5 [c]	3.8	**4.6**	NA	**2.3**	3.3
PD 6 [c]	3.7	NA	NA	**2.4**	3.5
Day 71/85 [d]	4.2	4.0	NA	**1.9**	4.1
Day 98	**4.6**	NA	NA	NA	NA
Day 112	NA	NA	NA	**2.5**	3.7
Day 126	**4.4**	NA	NA	**2.8**	4.0
Day 133	**4.8**	NA	NA	3.3	4.1
Total Protein (g/dL)					
Pre-dose	8.0	7.5	**6.3**	7.4	7.3
PD 1 [c]	7.4	7.3	NA	7.1	7.5
PD 2 [c]	7.5	7.2	NA	**6.4**	6.9
PD 3 [c]	6.8	NA	NA	**6.2**	6.6
PD 4 [c]	6.7	NA	NA	**6.2**	**6.4**
PD 5 [c]	6.6	6.8	NA	**5.9**	6.5
PD 6 [c]	**6.4**	NA	NA	**6.2**	6.7
Day 71/85 [d]	**6.2**	6.9	NA	**6.1**	6.7
Day 98	6.9	NA	NA	NA	NA
Day 112	NA	NA	NA	**5.5**	**6.3**
Day 126	7.3	NA	NA	**5.9**	**6.2**
Day 133	7.9	NA	NA	**6.4**	6.5
Day 140	8.0	NA	NA	6.7	6.8

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Only individual values were provided in the report; the data is shown for key time points only. Values in bold are outside of the normal range of typical serum chemistry values shown in Mod4.2.3.2.2/8754-0701/TabE.

[c] Time points noted as PD are for 24 h post-dose samples.

[d] Day 71 for the group 1 animals; Day 85 for the group 2 animals, ie, 29 days after Dose 6.

F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; No. = number; PD = post-dose

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5			0→25
No. of Animals	M:1	F:2		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Serum Chemistry(Continued) [b]					
IgM (mg/dL)					
Pre-dose	45.0	99.0	107.0	75.0	77.0
PD 1 [c]	31.0	76.0	NA	43.0	59.0
PD 2 [c]	32.0	64.0	NA	19.0	33.0
PD 3 [c]	**<10.0**	NA	NA	10.0	29.0
PD 4 [c]	14.0	NA	NA	**<10.0**	**<10.0**
PD 5 [c]	15.0	44.0	NA	**<10.0**	12.0
PD 6 [c]	**<10.0**	NA	NA	**<10.0**	**<10.0**
Day 71/85 [d]	**<10.0**	**<0.2**	NA	23.0	14.0
Day 98	14.0	NA	NA	NA	NA
Day 112	NA	NA	NA	18.0	25.0
Day 126	10.0	NA	NA	15.0	17.0
Day 133	15.0	NA	NA	**<10.0**	21.0
Day 140	21.0	NA	NA	20.0	14.0
Day 147	15.0	NA	NA	17.0	16.0

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Only individual values were provided in the report; the data is shown for key time points only. Values in bold are outside of the normal range of typical serum chemistry values shown in Mod4.2.3.2.2/8754-0701/TabE.

[c] Time points noted as PD are for 24 h post-dose samples.

[d] Day 71 for the group 1 animals; Day 85 for the group 2 animals, ie, 29 days after Dose 6.

F = female; h = hour; ID = identification; IgM = immunoglobulin M; IV = intravenous; M = male; NA = not applicable; No. = number; PD = post-dose

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1	F:2		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Serum Chemistry (Continued) [b]					
IgG (mg/dL)					
Pre-dose	1598.0	1948.0	1470.0	1661.0	1309.0
PD 1 [c]	1590.0	1766.0	NA	1585.0	1198.0
PD 2 [c]	1167.0	1416.0	NA	1225.0	970.0
PD 3 [c]	968.0	NA	NA	993.0	900.0
PD 4 [c]	**835.0**	NA	NA	871.0	**681.0**
PD 5 [c]	**798.0**	953.0	NA	**824.0**	**831.0**
PD 6 [c]	**634.0**	NA	NA	894.0	**799.0**
Day 71/85 [d]	**612.0**	1114.0	NA	**638.0**	**638.0**
Day 98	**713.0**	NA	NA	NA	NA
Day 112	NA	NA	NA	**618.0**	**587.0**
Day 126	1244.0	NA	NA	**557.0**	**676.0**
Day 133	1488.0	NA	NA	**599.0**	**611.0**
Day 140	1523.0	NA	NA	**761.0**	**669.0**
Day 147	1442.0	NA	NA	**781.0**	**730.0**

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Only individual values were provided in the report; the data is shown for key time points only. Values in bold are outside of the normal range of typical serum chemistry values shown in Mod4.2.3.2.2/8754-0701/TabE.

[c] Time points noted as PD are for 24 h post-dose samples.

[d] Day 71 for the group 1 animals; Day 85 for the group 2 animals, ie, 29 days after Dose 6.

F = female; h = hour; ID = identification; IgG = immunoglobulin G; IV = intravenous; M = male; NA = not applicable; No. = number; PD = post-dose

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5			0→25
No. of Animals	M:1	F:2		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Serum Chemistry (Continued) [b]					
C-reactive protein (mg/dL)					
Pre-dose	**<0.2**	**<0.2**	**<0.2**	**<0.2**	**<0.2**
PD 1 [c]	**11.2**	**12.8**	NA	**9.0**	**16.4**
PD 2 [c]	0.5	1.6	NA	1.9	1.2
PD 3 [c]	1.0	NA	NA	**6.4**	**16.7**
PD 4 [c]	2.7	NA	NA	**17.9**	**9.3**
PD 5 [c]	2.5	**0.1**	NA	**15.8**	**6.2**
PD 6 [c]	1.9	NA	NA	**13.7**	**7.5**
Day 71/85 [d]	**<0.2**	**<0.2**	NA	**5.9**	**<0.2**
Day 98	**<0.2**	NA	NA	NA	NA
Day 112	NA	NA	NA	0.3	0.7
Day 126	**<0.2**	NA	NA	1.5	**<0.2**
Day 133	**<0.2**	NA	NA	0.7	**<0.2**
Day 140	**<0.2**	NA	NA	0.2	**<0.2**
Day 147	**<0.2**	NA	NA	0.8	**<0.2**

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Only individual values were provided in the report; the data is shown for key time points only. Values in bold are outside of the normal range of typical serum chemistry values shown in Mod4.2.3.2.2/8754-0701/TabE.

[c] Time points noted as PD are for 24 h post-dose samples.

[d] Day 71 for the group 1 animals; Day 85 for the group 2 animals, ie, 29 days after Dose 6.

F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; No. = number; PD = post-dose

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5			0→25
No. of Animals	M:1		F:2	M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Urinalysis	-	-	-	-	-
Direct Antiglobulin Test	-	-	-	-	-
Gross Pathology [b]					
Number Examined	0	0	1	0	0
Foamy liquid (mouth and nares)			P		
Lungs, over inflation and edema			P		
Lung, foci of anthracosis			P		
Heart, left ventricle: thickening			P		
Heart, right ventricle: presence of chronic infarct (scar)/area of devitalized red tissue			P (10 cm)		
Stomach/intestines: adhesions			P		
Histopathology [b]					
Number Examined	0	0	1	0	0
Lung, peribronchiolar edema			P		

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Gross and histopathology examinations were only performed for animal No. 92A016, which died shortly after receiving the first IV infusion of 5 mg/kg daratumumab.

F = female; h =hour; ID = identification; IV = intravenous; M = male; NA = not applicable; No. = number; P = finding present; - = No noteworthy findings

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5			0→25
No. of Animals	M:1		F:2	M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Additional Examinations					
Serum cytokine analysis [b]	NA	NA		NA	NA
TNF-α (pg/mL)					
Day 35 (1.5 h post-Dose 1)			699		
Day 35 (prior to terminal necropsy)			389		
IFN-γ (pg/mL)					
Day 35 (1.5 h post-Dose 1)			1070		
Day 35 (prior to terminal necropsy)			BLLOQ		
IL-6 (pg/mL)					
Day 35 (1.5 h post dose)			29581		
Day 35 (prior to terminal necropsy)			33128		
Bone marrow aspirates [c]	NE	NE	NE	NE	NE
Lymph node biopsies	-	-	-	-	-
Skin biopsies	-	-	-	-	-

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Blood samples were obtained from animal No. 92A016 only on Day 25 (pre-study), Day 35 (pre-dose Dose 1), and on Day 35 (post-dose, 1.5 h post-dose, and prior to terminal necropsy for the determination of serum cytokines TNF-α, IL-6, and IFN-γ. Samples were all BLLOQ (ie, below 25 pg/mL) for Day 25, and for Day 35 (pre-dose and immediately post-dose Dose 1).

[c] Aspirates were of poor quality and thus could not be evaluated.

BLLOQ = below the lower limit of quantitation; F = female; h =hour; ID = identification; IFN-γ = interferon-gamma; IL-6 = interleukin-6; IV = intravenous; M = male; NA = not applicable; NE = not evaluated; No. = number; TNF-α = Tumor Necrosis Factor-alpha; - = No noteworthy findings

(Continued)

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1	F:2		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Additional Examinations					
Flow Cytometry [b]					
Peripheral Blood:					
T-Lymphocytes					
T-Helper Lymphocytes Binding to Dara (CD45+/CD3+/CD4+/Dara+) [cells/µL]					
Predose	567	230	399	673	358
Day 8/23 (PD 1) [c,d]	297	101	NA	306	260
Day 14/28 (Pre-D 2) [c,d]	225	220	NA	408	226
Day 21/35 (Pre-D 3) [c,d]	235	NA	NA	247	144
Day 28/42 (Pre-D 4) [c,d]	206	NA	NA	443	185
Day 35/49 (Pre-D 5) [c,d]	180	NA	NA	354	162
Day 36	NA	422	NA	NA	NA
Day 42/56 (Pre-D 6) [c,d]	232	286	NA	559	247
Day 57	120	NA	NA	NA	NA
Day 71	109	342	NA	337	248
Day 84/85	733	NA	NA	301	388
Day 98	442	NA	NA	247	270
Day 112	NA	NA	NA	234	222
Day 126	350	NA	NA	258	274
Day 133	565	NA	NA	245	223
Day 140	470	NA	NA	206	258
Day 147	390	NA	NA	330	278
NK Cells					
NK Cells Binding to Dara (CD45+/CD56+/CD3-/Dara+) [cells/µL]					
Pre-dose	273	181	350	335	387
Day 98	217	NA	NA	309	244
Day 112	NA	NA	NA	247	287
Day 126	335	NA	NA	218	204
Day 133	447	NA	NA	139	135
Day 140	225	NA	NA	157	130
Day 147	189	NA	NA	160	134

(Continued)

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.
[b] Only individual values were provided in the report; the data is shown for key time points only.
[c] For flow cytometry, time points noted as Pre-D are for pre-dose samples; time points noted as PD are for 24 h post-dose samples.
[d] Day X/X indicates the study day for the Group 1 animals, followed by the study day for the Group 2 animals.

Dara = daratumumab; F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; NK = natural killer; No. = number; PD = post-dose; Pre-D = pre-dose

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1	F:2		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Additional Examinations					
Flow Cytometry (Continued) [b]					
Peripheral Blood:					
B-Lymphocytes					
B-Lymphocytes (CD20+) [cells/µL]					
Pre-dose	777	390	270	712	194
Day 21/35 (Pre-D 3) [c,d]	313	NA	NA	365	138
Day 28/42 (Pre-D 4) [c,d]	222	NA	NA	279	124
Day 35/49 (Pre-D 5) [c,d]	255	NA	NA	237	114
B-Lymphocytes Binding to Dara (CD45+/CD20+/Dara+) [cells/µL]					
Pre-dose	778	388	271	707	192
Day 21/35 (Pre-D 3) [c,d]	304	NA	NA	359	134
Day 28/42 (Pre-D 4) [c,d]	212	NA	NA	280	118
Day 35/49 (Pre-D 5) [c,d]	242	294	NA	234	112
Plasma Cells	-	-	-	-	-

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.
[b] Only individual values were provided in the report; the data is shown for key time points only.
[c] For flow cytometry, time points noted as Pre-D are for pre-dose samples.
[d] Day X/X indicates the study day for the Group 1 animals, followed by the study day for the Group 2 animals.

Dara = daratumumab; F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; No. = number; Pre-D = pre-dose; - = No noteworthy findings

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1	F:2		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Additional Examinations					
Flow Cytometry (Continued) [b]					
Peripheral Blood:					
Monocytes					
Monocytes Not Binding to Dara (Monocyte Gating):					
Monocytes Not Expressing CD4 (CD45+/CD14+/CD4-) [cells/μL]					
Pre-dose Vehicle [c]	NA	NA	52	32	11
Day 8/23 (PD 1) [d,e]	35	14	NA	32	51
Day 14/28 (Pre-D 2) [d,e]	7	30	NA	31	25
Day 21/35 (Pre-D 3) [d,e]	7	NA	NA	48	29
Day 28/42 (Pre-D 4) [d,e]	22	NA	NA	123	49
Day 35/49 (Pre-D 5) [d,e]	6	NA	NA	119	22
Day 84/85 [e]	5	NA	NA	10	5
Day 98	4	NA	NA	60	5
Day 112	NA	NA	NA	4	5
Day 126	4	NA	NA	7	3
Day 133	3	NA	NA	6	3
Day 140	2	NA	NA	9	4
Day 147	3	NA	NA	5	3

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.
[b] Only individual values were provided in the report; the data is shown for key time points only.
[c] The pre-dose (ie, pre-trial) value is not provided as there was no information available for that time point; therefore, the pre-dose vehicle value was provided for purpose of comparison.
[d] For flow cytometry, time points noted as Pre-D are for pre-dose samples; time points noted as PD are for 24 h post-dose samples.
[e] Day X/X indicates the study day for the Group 1 animals, followed by the study day for the Group 2 animals.

Dara = daratumumab; F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; No. = number; PD = post-dose; Pre-D = pre-dose

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1	F:2		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Additional Examinations					
Flow Cytometry (Continued) [b]					
Peripheral Blood:					
Monocytes					
Monocytes Binding to Dara (Monocyte Gating):					
Monocytes Expressing CD4 and Binding to Dara (CD45+/CD14+/CD4+Dara+) [cells/μL]					
Pre-dose Vehicle[c]	NA	NA	1296	579	214
Day 7/22/35 (Pre-D 1) [d,e]	255	438	1687	1724	617
Day 8/23 (PD 1)[d,e]	366	148	NA	2610	255
Day 14/28 (Pre-D 2) [d,e]	228	388	NA	1457	323
Day 21/35 (Pre-D 3) [d,e]	266	NA	NA	2446	739
Day 28/42 (Pre-D 4) [d,e]	911	NA	NA	5013	791
Day 35/49 (Pre-D 5) [d,e]	2718	NA	NA	878	247
Day 36	NA	790	NA	NA	NA
Day 43	NA	334	NA	NA	NA
Day 42/56 (Pre-D 6) [d,e]	6169	190	NA	780	306
Day 57	13625	NA	NA	NA	NA
Day 71	621	190	NA	923	1286
Day 84/85 [e]	4757	NA	NA	1082	384
Day 98	448	NA	NA	807	338

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Only individual values were provided in the report; the data is shown for key time points only.

[c] The pre-dose (ie, pre-trial) value is not provided as there was no information available for that time point; therefore, the pre-dose vehicle value was provided for purpose of comparison.

[d] For flow cytometry, time points noted as Pre-D are for pre-dose samples; time points noted as PD are for 24 h post-dose samples.

[e] Day X/X indicates the study day for the Group 1 animals, followed by the study day for the Group 2 animals; Day X/X/X indicates the study day for the Group 1 male and female (No. 96A009 and 95A015) originally on test, followed by the study day for the Group 2 then by the study day for the Group 1 replacement female animals.

Dara = daratumumab; F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; No. = number; PD = post-dose; Pre-D = pre-dose

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1		F:2	M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Additional Examinations					
Flow Cytometry (Continued) [b]					
Peripheral Blood:					
Monocytes					
Monocytes Binding to Dara (Monocyte Gating):					
Monocytes Not Expressing CD4 but Binding to Dara (CD45+/CD14+/CD4-Dara+) [cells/µL]					
Pre-dose Vehicle [c]	NA	NA	4073	10735	1391
Day 7/22/35 (Pre-D 1) [d,e]	840	1500	13798	25028	9916
Day 8/23 (PD 1) [d,e]	1247	754	NA	13236	7980
Day 14/28 (Pre-D 2) [d,e]	6389	15971	NA	5596	4592
Day 21/35 (Pre-D 3) [d,e]	2866	NA	NA	4155	5106
Day 28/42 (Pre-D 4) [d,e]	5027	NA	NA	12323	12221
Day 35/49 (Pre-D 5) [d,e]	2459	NA	NA	7173	3139
Day 36	NA	5334	NA	NA	NA
Day 43	NA	6960	NA	NA	NA
Day 42/56 (Pre-D 6) [d,e]	12779	4923	NA	7279	7120
Day 57	1098	NA	NA	NA	NA
Day 71	2150	3108	NA	5585	9530
Day 84/85 [e]	4162	NA	NA	7199	9651

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.
[b] Only individual values were provided in the report; the data is shown for key time points only.
[c] The pre-dose (ie, pre-trial) value is not provided as there was no information available for that time point; therefore, the pre-dose vehicle value was provided for purpose of comparison.
[d] For flow cytometry, time points noted as Pre-D are for pre-dose samples; time points noted as PD are for 24 h post-dose samples.
[e] Day X/X indicates the study day for the Group 1 animals, followed by the study day for the Group 2 animals; Day X/X/X indicates the study day for the Group 1 male and female (No. 96A009 and 95A015) originally on test, followed by the study day for the Group 2 then by the study day for the Group 1 replacement female animals.

Dara = daratumumab; F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; No. = number; PD = post-dose; Pre-D = pre-dose

(Continued)

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1		F:2	M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Additional Examinations					
Flow Cytometry (Continued) [b]					
Peripheral Blood:					
Monocytes					
Monocytes Not Binding to Dara (Lymphocyte Gating):					
Monocytes Not Binding to Dara (CD45+/CD14+/Dara-) [cells/μL]					
Pre-dose Vehicle[c]	NA	NA	2	7	2
Day 7/22/35 (Pre-D 1) [d,e]	1	3	7	8	9
Day 8/23 (PD 1)[d,e]	3	1	NA	8	7
Day 14/28 (Pre-D 2) [d,e]	5	3	NA	8	7
Day 21/35 (Pre-D 3) [d,e]	2	NA	NA	8	9
Day 28/42 (Pre-D 4) [d,e]	5	NA	NA	4	7
Day 35/49 (Pre-D 5) [d,e]	7	NA	NA	1	1
Day 36	NA	8	NA	NA	NA
Day 43	NA	7	NA	NA	NA
Day 42/56 (Pre-D 6) [d,e]	8	3	NA	3	2
Day 57	9	NA	NA	NA	NA
Day 71	2	5	NA	4	5
Day 84/85 [e]	2	NA	NA	3	2
Day 98	1	NA	NA	1	2
Day 112	NA	NA	NA	1	2
Day 126	2	NA	NA	3	3
Day 133	1	NA	NA	0	2
Day 140	1	NA	NA	1	3
Day 147	NA	NA	NA	2	1

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Only individual values were provided in the report; the data is shown for key time points only.

[c] The pre-dose (ie, pre-trial) value is not provided as there was no information available for that time point; therefore, the pre-dose vehicle value was provided for purpose of comparison.

[d] For flow cytometry, time points noted as Pre-D are for pre-dose samples; time points noted as PD are for 24 h post-dose samples.

[e] Day X/X indicates the study day for the Group 1 animals, followed by the study day for the Group 2 animals; Day X/X/X indicates the study day for the Group 1 male and female (No. 96A009 and 95A015) originally on test, followed by the study day for the Group 2 then by the study day for the Group 1 replacement female animals.

Dara = daratumumab; F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; No. = number; PD = post-dose; Pre-D = pre-dose

(Continued)

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1	F:2		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Additional Examinations					
Flow Cytometry (Continued) [b]					
Peripheral Blood:					
Monocytes					
Monocytes Binding to Dara (Lymphocyte Gating):					
Monocytes Binding to Dara (CD45+/CD14+/Dara+) [cells/µL]					
Pre-dose Vehicle[c]	NA	NA	8	62	15
Day 7/22/35 (Pre-D 1) [d,e]	16	18	32	24	28
Day 8/23 (PD 1) [d,e]	15	13	NA	37	26
Day 14/28 (Pre-D 2) [d,e]	48	27	NA	38	28
Day 21/35 (Pre-D 3) [d,e]	29	NA	NA	35	22
Day 28/42 (Pre-D 4) [d,e]	18	NA	NA	22	20
Day 35/49 (Pre-D 5) [d,e]	26	NA	NA	7	3
Day 36	NA	48	NA	NA	NA
Day 43	NA	18	NA	NA	NA
Day 42/56 (Pre-D 6) [d,e]	60	8	NA	10	7
Day 57	23	NA	NA	NA	NA
Day 71	6	15	NA	12	11
Day 84/85 [e]	21	NA	NA	6	7
Day 98	12	NA	NA	26	16
Day 112	NA	NA	NA	12	7
Day 126	29	NA	NA	11	21
Day 133	6	NA	NA	7	8
Day 140	12	NA	NA	7	12
Day 147	NA	NA	NA	10	11

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.
[b] Only individual values were provided in the report; the data is shown for key time points only.
[c] The pre-dose (ie, pre-trial) value is not provided as there was no information available for that time point; therefore, the pre-dose vehicle value was provided for purpose of comparison.
[d] For flow cytometry, time points noted as Pre-D are for pre-dose samples; time points noted as PD are for 24 h post-dose samples.
[e] Day X/X indicates the study day for the Group 1 animals, followed by the study day for the Group 2 animals; Day X/X/X indicates the study day for the Group 1 male and female (No. 96A009 and 95A015) originally on test, followed by the study day for the Group 2 then by the study day for the Group 1 replacement female animals.

Dara = daratumumab; F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; No. = number; PD = post-dose; Pre-D = pre-dose

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1	F:2		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Additional Examinations					
Flow Cytometry (Continued) [b]					
Peripheral Blood:					
Monocytes					
Monocytes Binding to Dara (Lymphocyte Gating):					
Monocytes Expressing CD4 and Binding to Dara (CD45+/CD14+/CD4+/Dara+) [cells/µL]					
Pre-dose Vehicle [c]	NA	NA	396	250	184
Day 7/22/35 (Pre-D 1) [d,e]	254	438	229	48	320
Day 8/23 (PD 1) [d,e]	356	114	NA	175	131
Day 14/28 (Pre-D 2) [d,e]	157	199	NA	157	117
Day 21/35 (Pre-D 3) [d,e]	138	NA	NA	215	78
Day 28/42 (Pre-D 4) [d,e]	298	NA	NA	239	57
Day 35/49 (Pre-D 5) [d,e]	119	NA	NA	67	14
Day 36	NA	439	NA	NA	NA
Day 43	NA	211	NA	NA	NA
Day 42/56 (Pre-D 6) [d,e]	169	134	NA	93	92
Day 57	739	NA	NA	NA	NA
Day 71	54	94	NA	96	103
Day 84/85 [e]	190	NA	NA	54	61
Day 98	144	NA	NA	237	87
Day 112	NA	NA	NA	40	57
Day 126	123	NA	NA	112	78
Day 133	115	NA	NA	133	82
Day 140	111	NA	NA	167	103
Day 147	NA	NA	NA	118	61

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Only individual values were provided in the report; the data is shown for key time points only.

[c] The pre-dose (ie, pre-trial) value is not provided as there was no information available for that time point; therefore, the pre-dose vehicle value was provided for purpose of comparison.

[d] For flow cytometry, time points noted as Pre-D are for pre-dose samples; time points noted as PD are for 24 h post-dose samples.

[e] Day X/X indicates the study day for the Group 1 animals, followed by the study day for the Group 2 animals; Day X/X/X indicates the study day for the Group 1 male and female (No. 96A009 and 95A015) originally on test, followed by the study day for the Group 2 then by the study day for the Group 1 replacement female animals.

Dara = daratumumab; F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; No. = number; PD = post-dose; Pre-D = pre-dose

(Continued)

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1	F:2		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Additional Examinations					
Flow Cytometry (Continued) [b]					
Peripheral Blood:					
Monocytes					
Monocytes Binding to Dara (Lymphocyte Gating):					
Monocytes Not Expressing CD4 but Binding to Dara (CD45+/CD14+/CD4-/Dara+) [cells/µL]					
Pre-dose Vehicle [c]	NA	NA	417	2095	797
Day 7/22/35 (Pre-D 1) [d,e]	840	1500	1350	692	1735
Day 8/23 (PD 1) [d,e]	952	300	NA	773	481
Day 14/28 (Pre-D 2) [d,e]	3100	1594	NA	448	209
Day 21/35 (Pre-D 3) [d,e]	322	NA	NA	372	145
Day 28/42 (Pre-D 4) [d,e]	476	NA	NA	1075	511
Day 35/49 (Pre-D 5) [d,e]	346	NA	NA	219	19
Day 36	NA	905	NA	NA	NA
Day 43	NA	737	NA	NA	NA
Day 42/56 (Pre-D 6) [d,e]	2581	389	NA	216	110
Day 57	992	NA	NA	NA	NA
Day 71	20	307	NA	148	149
Day 84/85	522	NA	NA	200	184
Day 98	22	NA	NA	271	33
Day 112	NA	NA	NA	53	134
Day 126	58	NA	NA	42	36
Day 133	24	NA	NA	33	15
Day 140	20	NA	NA	38	23
Day 147	NA	NA	NA	32	19

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Only individual values were provided in the report; the data is shown for key time points only.

[c] The pre-dose (ie, pre-trial) value is not provided as there was no information available for that time point; therefore, the pre-dose vehicle value was provided for purpose of comparison.

[d] For flow cytometry, time points noted as Pre-D are for pre-dose samples; time points noted as PD are for 24 h post-dose samples.

[e] Day X/X indicates the study day for the Group 1 animals, followed by the study day for the Group 2 animals; Day X/X/X indicates the study day for the Group 1 male and female (No. 96A009 and 95A015) originally on test, followed by the study day for the Group 2 then by the study day for the Group 1replacement female animals.

Dara = daratumumab; F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; No. = number; PD = post-dose; Pre-D = pre-dose

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1		F:2	M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Additional Examinations					
Flow Cytometry (Continued)					
Peripheral Blood:					
White Blood Cells	-	-	-	-	-

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

F = female; h = hour; ID = identification; IV = intravenous; M = male; No. = number; - = No noteworthy findings

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1	F:2 [a]		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Additional Examinations					
Flow Cytometry (Continued) [b]					
Bone Marrow:					
T-Lymphocytes	-	-	-	-	-
NK Cells	-	-	-	-	-
B-Lymphocytes	-	-	-	-	-
Plasma Cells	-	-	-	-	-
Stem Cells	-	-	-	-	-
White Blood Cells	-	-	-	-	-
Monocytes					
Monocytes Not Binding to Dara (Monocyte Gating):					
Monocytes Not Binding to Dara (CD45+/CD14+/Dara-) [% in region]					
Day 23/36/37 [c,d]	27.70	0.38	NA	0.65	3.44
Day 43/57 [c]	22.09	NA	NA	0.81	18.10
Day 71/85 [c]	3.55	0.78	NA	1.07	3.47
Day 98	5.20	NA	NA	NA	NA
Day 112	NA	NA	NA	2.68	10.40
Day 126	7.82	NA	NA	2.01	9.86
Day 147	2.74	NA	NA	0.04	0.63

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Only individual values were provided in the report; the data is shown for key time points only.

[c] Day X/X indicates the study day for the Group 1 animals, followed by the study day for the Group 2 animals; Day X/X/X indicates the study day for the Group 1 male and female (No. 96A009 and 95A015) originally on test, followed by the study day for the Group 1 replacement female then by the study day for the Group 2 animals.

[d] The pre-dose (ie, pre-trial) value is not provided as there was no information available at that time point for all animals; therefore, the Day 23/36/37 data has been provided for purpose of comparison.

Dara = daratumumab; F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; NK = natural killer; No. = number; - = No noteworthy findings

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1		F:2	M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Additional Examinations					
Flow Cytometry (Continued) [b]					
Bone Marrow:					
Monocytes					
Monocytes Binding to Dara (Monocyte Gating):					
Monocytes Binding to Dara (CD45+/CD14+/Dara+) [% in region]					
Day 23/36/37 [c,d]	41.83	38.90	NA	51.46	32.21
Day 71/85 [c]	9.14	27.96	NA	19.48	7.60
Day 98	20.13	NA	NA	NA	NA
Day 112	NA	NA	NA	38.07	24.43
Day 126	31.44	NA	NA	25.14	16.34
Day 147	30.29	NA	NA	39.23	22.06

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Only individual values were provided in the report; the data is shown for key time points only.

[c] Day X/X indicates the study day for the Group 1 animals, followed by the study day for the Group 2 animals; Day X/X/X indicates the study day for the Group 1 male and female (No. 96A009 and 95A015) originally on test, followed by the study day for the Group 1 replacement female then by the study day for the Group 2 animals.

[d] The pre-dose (ie, pre-trial) value is not provided as there was no information available at that time point for all animals; therefore, the Day 23/36/37 data has been provided for purpose of comparison.

Dara = daratumumab; F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; No. = number

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1		F:2	M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Additional Examinations					
Flow Cytometry (Continued) [b]					
Bone Marrow:					
Monocytes					
Monocytes Not Binding to Dara (Lymphocyte Gating):					
Monocytes Not Binding to Dara (CD45+/CD14+/Dara-) [% in region]					
Day 23/36/37 [c,d]	1.83	0.38	NA	0.53	0.45
Day 43/57 [c]	2.32	NA	NA	0.12	0.18
Day 71/85 [c]	0.17	0.05	NA	0.02	0.04
Day 98	0.04	NA	NA	NA	NA
Day 112	NA	NA	NA	0.07	0.04
Day 126	0.11	NA	NA	0.13	0.09
Day 147	0.13	NA	NA	0.08	0.04

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Only individual values were provided in the report; the data is shown for key time points only.

[c] Day X/X indicates the study day for the Group 1 animals, followed by the study day for the Group 2 animals; Day X/X/X indicates the study day for the Group 1 male and female (No. 96A009 and 95A015) originally on test, followed by the study day for the Group 1 replacement female then by the study day for the Group 2 animals.

[d] The pre-dose (ie, pre-trial) value is not provided as there was no information available for that time point for all animals; therefore, the Day 23/36/37 data has been provided for purpose of comparison.

Dara = daratumumab; F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; No. = number

(Continued)

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1	F:2		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Additional Examinations					
Flow Cytometry (Continued) [b]					
Bone Marrow:					
Monocytes					
Monocytes Binding to Dara (Lymphocyte Gating):					
Monocytes Binding to Dara (CD45+/CD14+/Dara+) [% in region]					
Day 23/36/37 [c,d]	4.06	3.27	NA	1.49	1.19
Day 43/57 [c]	4.51	NA	NA	2.39	0.91
Day 71/85 [c]	0.76	0.51	NA	0.51	0.84
Day 98	0.94	NA	NA	NA	NA
Lymph Node:					
B-Lymphocytes	-	-	-	-	-
Plasma Cells	-	-	-	-	-
T-Lymphocytes					
T-Helper Lymphocytes Binding to Dara (CD45+/CD3+/CD4+/Dara+) [% in region]					
Pre-dose	31.62	17.29	18.05	22.11	30.50
Day 43/57 [c]	18.60	NA	NA	1.63	2.62
Day 71/85 [c]	7.49	15.45	NA	9.03	8.12
Day 112	NA	NA	NA	12.10	9.13
Day 126	24.85	NA	NA	6.03	3.39
Day 147	20.43	NA	NA	15.43	24.30
T-Cytotoxic/Suppressor Lymphocytes Binding to Dara (CD45+/CD3+/CD8+/Dara+) [% in region]					
Pre-dose	24.53	19.79	10.56	13.57	20.25
Day 43/57 [c]	14.76	NA	NA	3.87	6.22

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Only individual values were provided in the report; the data is shown for key time points only.

[c] Day X/X indicates the study day for the Group 1 animals, followed by the study day for the Group 2 animals; Day X/X/X indicates the study day for the Group 1 male and female (No. 96A009 and 95A015) originally on test, followed by the study day for the Group 1 replacement female then by the study day for the Group 2 animals.

[d] The pre-dose (ie, pre-trial) value is not provided as theer was no information available for that time point for all animals; therefore, the Day 23/36/37 data has been provided for purpose of comparison.

Dara = daratumumab; F = female; h = hour; ID = identification; IV = intravenous; M = male; NA = not applicable; No. = number; - = No noteworthy findings

(Continued)

2.6.7.7 反復投与毒性試験（続き）

Report Title: Multiple Dose Safety Study in Chimpanzees with a 2-Month Recovery Period **Test Article:** Daratumumab

DOSING AND RECOVERY PERIOD					
Dose (mg/kg/week)		0→5		0→25	
No. of Animals	M:1	F:2		M:1	F:1
Animal ID No.	96A009	95A015 [a]	92A016 [a]	96A015	96A017
Noteworthy Findings					
Additional Examinations					
Flow Cytometry (Continued) [b]					
Lymph Node:					
NK Cells					
NK Cells Binding to Dara (CD45+/CD56+/CD3-/Dara+) [% in region]					
Pre-dose	71.78	68.02	60.47	60.69	61.30
Day 43/57 [c]	52.90	NA	NA	13.75	13.41
Day 71/85 [c]	50.14	72.28	NA	29.68	17.87
Day 98	66.08	NA	NA	NA	NA
Day 112	NA	NA	NA	25.85	18.26
Day 126	57.19	NA	NA	41.95	38.94
Day 147	44.87	NA	NA	61.23	53.92
White Blood Cells					
White Blood Cells (Lymphocyte Gating):					
White Blood Cells Binding to Dara (CD45+/Dara+) [% in region]					
Pre-dose	73.39	66.95	75.79	68.28	69.49
Day 23/36/37 [c]	18.71	50.26	NA	10.98	25.72
Day 43/57 [c]	19.22	NA	NA	7.65	4.82
Day 71/85 [c]	11.61	52.36	NA	64.79	14.90
Day 98	64.82	NA	NA	NA	NA
Day 112	NA	NA	NA	36.62	24.00
Day 126	68.74	NA	NA	21.09	14.70
Day 147	64.02	NA	NA	62.36	71.86

[a] Prior to doing on Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of the test compound, and died 1.5 h after the first dose.

[b] Only individual values were provided in the report; the data is shown for key time points only.

[c] Day X/X indicates the study day for the Group 1 animals, followed by the study day for the Group 2 animals; Day X/X/X indicates the study day for the Group 1 male and female (No. 96A009 and 95A015) originally on test, followed by the study day for the Group 1 replacement female then by the study day for the Group 2 animals.

Dara = daratumumab; F = female; h = hour; ID = identification; IV = intravenous; M = male; NK = natural killer; NA = not applicable; No. = number

2.6.7.8　*In Vitro* 遺伝毒性試験

該当資料なし

2.6.7.9　*In Vivo* 遺伝毒性試験

該当資料なし

2.6.7.10　がん原性試験

該当資料なし

2.6.7.11　生殖発生毒性試験：重要な試験以外の試験

該当資料なし

2.6.7.12　生殖発生毒性試験：受胎能及び着床までの初期胚発生に関する試験

該当資料なし

2.6.7.13　生殖発生毒性試験：胚・胎児発生に関する試験

該当資料なし

2.6.7.14　生殖発生毒性試験：出生前及び出生後の発生並びに母体の機能に関する試験

該当資料なし

2.6.7.15 新生児を用いた試験

該当資料なし

2.6.7.16 局所刺激性試験

該当資料なし

2.6.7.17　その他の毒性試験

Test Article: Daratumumab [a]

Species/Strain No. Per Group	Route (Vehicle/Formulation)	Duration of Dosing	Doses (μg/mL)	Noteworthy Findings	Study No./ Location in CTD
Other Studies					
Tissue Cross-Reactivity (GLP) Normal cynomolgus monkey tissue (3 donors/tissue)	*In vitro*	NA	0, 0.2, 0.5, 1 [b]	Specific HuMab-CD38-FITC staining was observed in the cytoplasm of blood vessels, bone marrow lymphocytes, cerebellum white matter, cerebrum white matter, cervix, colon lamina propria, fallopian tube interstitium, ileum lamina propria, lung alveolar cells, lymph node T-cells, peripheral nerve myelin, retina/choroidea glassy membrane, spinal cord white matter, spleen T-cell zone, stomach, striated muscle fibers, thymus T-cells in medulla and cortex, and tonsil T-cell zone. It was not possible to determine the subcellular location of specific staining in endothelial (capillary) cells, whose cytoplasm is particularly thin, or in the interstitium of glomeruli in the kidney or the sinusoids of the liver. In the kidney and liver, staining in the interstitium/sinusoids may reflect staining of endothelial cells.	510547/ 4.2.3.7.7.1
Tissue Cross-Reactivity (GLP) Normal chimpanzee tissue (1-2 donors; 1-2 tissues)	*In vitro*	NA	0.25, 1.25 [c]	Specific daratumumab-FITC staining occurred in the lymphoid cells and macrophages and hematopoietic cells in the spleen, tonsil, lymph nodes, and lamina propria of the intestinal tract. Specific binding was also detected in the cytoplasm of multiple chimpanzee tissues: adrenal gland, bone marrow, brain, colon, fallopian tube, gastrointestinal tract, heart, kidney, liver, lymph node, mesenteric lymph node, pancreas, pituitary, skin, spinal cord, spleen, striated muscle, testes, and tonsil. The only tissue examined that demonstrated no binding was lung.	BKV00003/ 4.2.3.7.7.2
Tissue Cross-Reactivity (GLP) Normal human tissue (3 donors/tissue)	*In vitro*	NA	0, 0.5, 1, 2 [c]	Specific daratumumab-FITC staining occurred in the lymphoid cells in the spleen, tonsil, lymph nodes, and thymus. Specific daratumumab binding was also detected in the cytoplasm of multiple human tissues, ie, capillaries of the pituitary gland, vascular endothelial cells of the fallopian tube, lymphocytes in the ileum serosa, parathyroid, lymph node, spleen, thymus and tonsil, kidney, testis, and thyroid interstitial cells, epithelial cells of the fallopian tube, and the prostate. The subcellular location of staining in vascular endothelial cells of the pituitary gland and fallopian tube could not be determined.	260571/ 4.2.3.7.7.3

[a] Studies were conducted with daratumumab unless otherwise specified.
[b] The study was conducted with HuMab-CD38 conjugated to FITC. HuMab-CD38 is a human IgG1 mAb that specifically binds to human and cynomolgus monkey CD38.
[c] Studies were conducted with daratumumab conjugated to FITC. Daratumumab is a human IgG1 mAb that specifically binds to human and chimpanzee CD38.

FITC = fluorescein isothiocyanate; GLP = Good Laboratory Practice; HuMab-CD38 = anti-cynomolgus CD38 mAb; IgG = immunoglobulin G; mAb = monoclonal antibody; NA = not applicable; No. = number